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STAPHYLOCOCCIC PNEUMONIA IN INFANTS: OCCURRENCE OF PNEUMOPYOTHORAX

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THE purpose of this article is to call attention to the severe nature of staphylococcic pneumonia in infants and to the occurrence of pneumopyothorax as a frequent complication in this disease.

Primary staphylococcic pneumonia is considered an uncommon disease in all age groups. Only a few reports appear in the literature concerning this affection, and most of these deal with staphylococcic pneumonia in adults. One of the earliest reports is that of Chickering and Park[1] in 1919 who pointed out the high mortality of this disease. A great number of their cases was associated with the influenza epidemic of 1918. Reimann[2] in 1933 reported a series of six cases of staphylococcic pneumonia, one of which was an infant 3 months of age.

The incidence of staphylococcic pneumonia in infants is fortunately low. In a series of pneumonias in children examined by Plummer, Raia, and Shultz,[3, 4] only 5 cases (1.6 per cent) out of a total number of 329 were due to a staphylococcic infection. Menten, Bailey, and DeBone[5] isolated the staphylococcus alone in 11 out of 131 cases of pneumonia in children which came to autopsy. In these last two reports no differentiation was made between primary and secondary staphylococcic infections of the lung.

In the clinical literature dealing with staphylococcic pneumonias in children, we find the report of Smith[6] who described an outbreak of staphylococcic pneumonias in newborn infants in a maternity hospital where 4 infants contracted this infection and succumbed. MacGregor[7] reported the autopsy findings of 10 cases of pneumonia in children under 2½ years of age, in which the staphylococcus was the sole or predominant pathogenic microorganism isolated. For the first time, apparently, pneumopyothorax was mentioned as a complication in 3 of these cases. Anderson and Cathcart[8] described 1 case of staphylococcic pneumonia complicated by soft tissue abscesses and osteomyelitis of the skull. This

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patient made a remarkable recovery. Kanof, Kramer, and Carnes[9] report a large series of cases, 2 patients of which developed a pneumopyothorax.

It seems advisable to subdivide staphylococcic pneumonias into primary and secondary groups.[2, 7, 9]

The primary group is comprised of those cases in which the infection is bronchiogenic in type, usually following an infection of the upper respiratory system, including the nasal accessory sinuses and the middle ear. These cases may show a transitory bacteremia.

The secondary group consists of cases in which the lung infection is metastatic, following a septicemia originating from a focus outside the respiratory tract. These cases, as a rule, show abscess formation in various organs of the body. Sepsis is the predominant feature, and osteomyelitis is the most frequent primary focus.

Only the primary group presents certain characteristic features and can be considered as a well-defined clinical and pathologic entity, as pointed out by Reimann.[2] For this reason our study comprises only cases which fall in this group.

In the reports concerning staphylococcic pneumonia in children, the occurrence of pneumopyothorax has been mentioned previously in only 5 cases.[7, 9] In none of these was the clinical, roentgenologic, and pathologic sequence of events demonstrated.

Following is the brief description of 6 cases of staphylococcic pneumonia in infants, in 4 of which the clinical, roentgenologic, and pathologic aspect of the complication of pneumopyothorax has been observed and studied.

CASE 1.—B. A. B. (No. A-7593), a white female infant, 1 years of age, was admitted to Grady Hospital Nov. 7, 1939, with the history of cold, cough, and fever of five days' duration. On admission the infant was restless and fretful and was breathing with difficulty. The temperature was 105°, the pulse rate, 145, and the respiration, 84. A chest examination revealed the findings of a consolidation in the left lower lobe, and a roentgenogram (Fig. 1) disclosed a fine hazy density in the left lower lung field, having the appearance of an early partial lobar consolidation.

Laboratory Findings.—The white blood count on admission was 12,400 with 58 per cent polymorphonuclear leucocytes; the red blood count was 3,700,000 with 65 per cent hemoglobin. Urinalysis showed 2 plus albumin with 2 to 3 pus cells per high power field. A throat culture revealed *Staphylococcus albus* as the predominating organism. A blood culture did not reveal any growth.

Course.—The patient was treated with sulfapyridine and received repeated blood transfusions. Despite this treatment the patient's course showed no improvement, and the temperature remained elevated between 103° and 105.5°. The pulse remained at a level of 160. Abdominal distention was very marked throughout the entire course. Three days after admission a second roentgenogram (Fig. 2*A*) revealed a pneumothorax on the left side with the complete collapse of the lung prevented by numerous folds and bands. The collapsed lung contained many air pockets which were interpreted as being abscess cavities within the lung parenchyma. A marked shifting of the heart to the right was noted. Following this roentgenogram

a thoracentesis was performed and a few cubic centimeters of reddish-brown fluid were obtained. On smear, gram-positive cocci resembling staphylococci morphologically were seen. On culture, hemolytic *Staph. aureus* was grown. The patient died four days after admission.

Autopsy.—

Essential Gross Findings: A displacement of the mediastinum to the right was noted. The left pleural cavity contained thick yellowish-brown purulent material. Straw-colored fluid was found in the right pleural cavity. The left lung was completely collapsed; the pleura was covered by a layer of yellowish fibrin. On cut section the lung presented a beefy red color. The right lung contained several areas of consolidation in the upper, middle, and lower lobes. The bronchi revealed a small amount of brownish serous fluid.

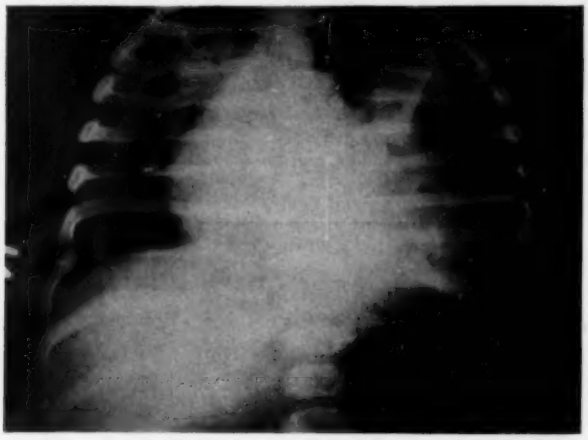
Fig. 1 (Case 1).—Admission date, Nov. 7, 1939; fine density in left lower lung field.

Microscopic Examination: The lungs showed confluent areas of consolidation in which the alveoli were filled with neutrophiles, large mononuclear cells, and some red blood cells. The fibrin layer of the pleura revealed infiltration of neutrophiles and some lymphocytes. There appeared dense masses of cocci, resembling staphylococci morphologically, in the walls of some of the abscesses (Fig. 2*B*).

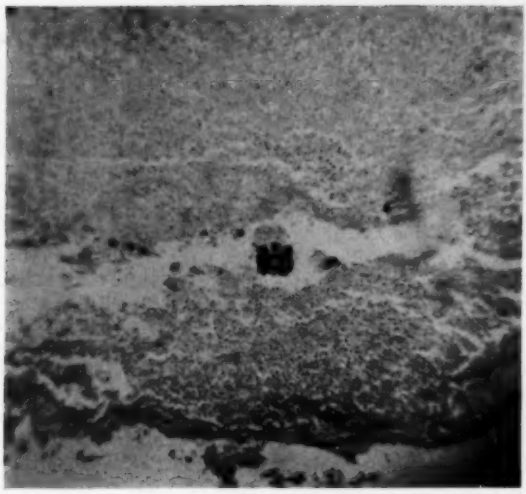
CASE 2.—H. E. L. (No. A-34176), a white male child, 16 months of age, was admitted to Grady Hospital April 25, 1940, with the history of a cough and fever for one week prior to admission. A roentgenogram (Fig. 3) on admission failed to reveal any chest pathology; nevertheless, the child was admitted to the ward because he presented the findings of an early lobar consolidation in the left lower lobe. The child was obviously critically ill, having rapid and labored respirations. The temperature on admission was 104.2°, the pulse rate, 130, the respiration, 35. Treatment was started with administration of sulfapyridine and continued with sulfamethylthiazole.

Laboratory Findings.—The white blood count was 27,600 with 90 per cent polymorphonuclear leucocytes. The red blood count was 5,900,000 with 73 per cent hemoglobin. On microscopic examination the urinalysis revealed 1 plus albumin with an occasional hyaline cast. Blood culture revealed *Bacillus subtilis,* but this was considered a contamination.

Course.—The day following admission, April 26, a second roentgenogram (Fig. 4) showed a diffuse density throughout the entire left hemithorax. There was possibly a slight shifting of the mediastinum to the left. In spite of intensive therapy the



A.



B.

Fig. 2 (Case 1).—Nov. 10, 1939, three days after admission. *A*, Pneumothorax on left side. Note adhesion in left upper lung field, preventing complete collapse of the lung. *B*, Photomicrograph of lung (low power). Note masses of staphylococci in center of abscess.

patient's condition became rapidly worse. Two days later further roentgenograms (Fig. 5*A*, supine position; Fig. 5*B*, upright position) were made, and collapse of the lung with free air and fluid in the pleural cavity was revealed. A thoracentesis was

performed and 40 c.c. of dark reddish-brown fluid were aspirated. Smears of the exudate showed gram-positive cocci in clumps, and cultures of the same material

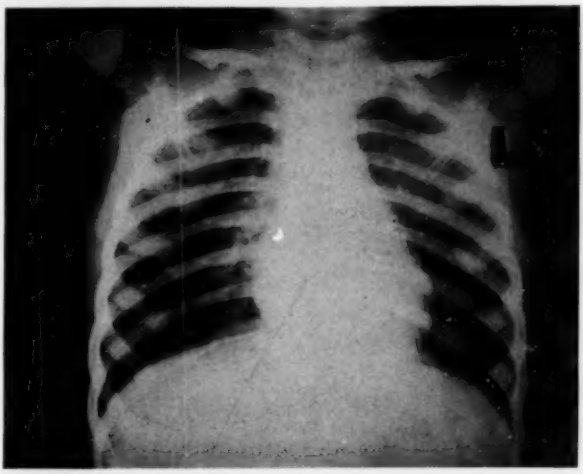


Fig. 3 (Case 2).—Admission date, April 25, 1940; normal chest roentgenogram.

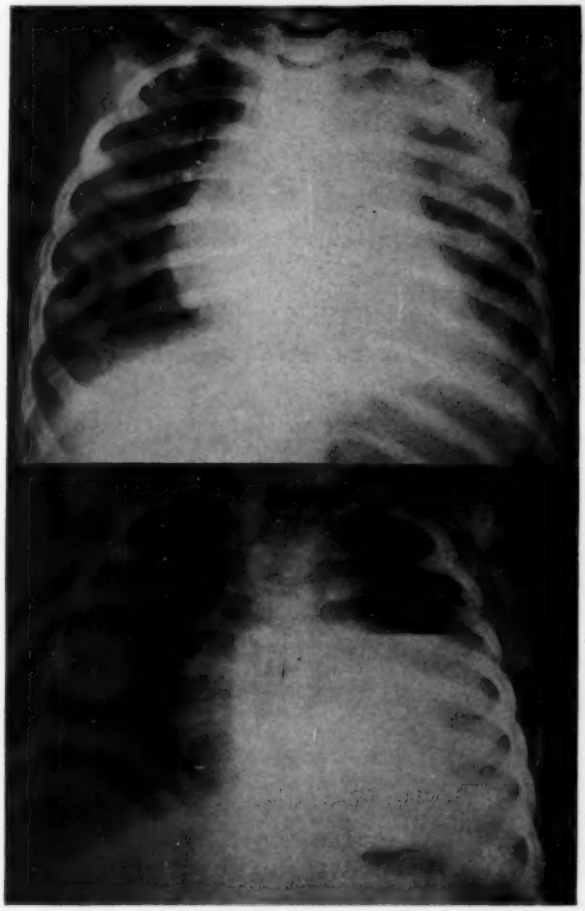
Fig. 4 (Case 2).—April 26, 1940, one day after admission; diffuse density in left lung field; consolidation; fluid?

revealed *Staph. aureus*. A closed surgical drainage was not deemed advisable because of the patient's critical condition. The patient died on the sixth hospital day.

Autopsy.—

Essential Gross Findings: The mediastinum was shifted to the right side and fixed in this position. The left lung was collapsed and there were about 100 c.c.

of sanguino-purulent material found in the left pleural cavity. The pleura was covered with thick, shaggy, yellowish fibrinous material. The lower lobe of the left lung contained in its lateral aspect an abscess which had ruptured into the pleural sac and was connected with a small bronchus. This cavity was filled with a small amount of purulent material. Scattered throughout the parenchyma of the left lung were small abscesses, varying in size from 0.5 to 2 cm. The right lung showed moderate hypostasis in its posterior portion. There was no evidence of tuberculosis.



A.

B.

Fig. 5 (Case 2).—*A*, April 28, 1940, three days after admission; pneumothorax on left side. Roentgenogram taken in supine position; no fluid level. *B*, Pneumothorax and pleural exudate on left side. Roentgenogram taken in upright position; fluid level clearly demonstrated.

Microscopic Examination: Sections through the left lung revealed a large number of small abscesses, the centers of which had undergone liquefaction necrosis. Numerous polymorphonuclear leucocytes and large mononuclear cells were found in the walls of these abscesses. In the center of these suppurative areas dense masses

of staphylococci were demonstrated (Fig. 6). Adjacent alveoli contained red blood cells, fine fibrin threads, and leucocytes. In the peripheral zone of a few larger abscesses an early proliferative reaction of the interstitial tissue was noted.

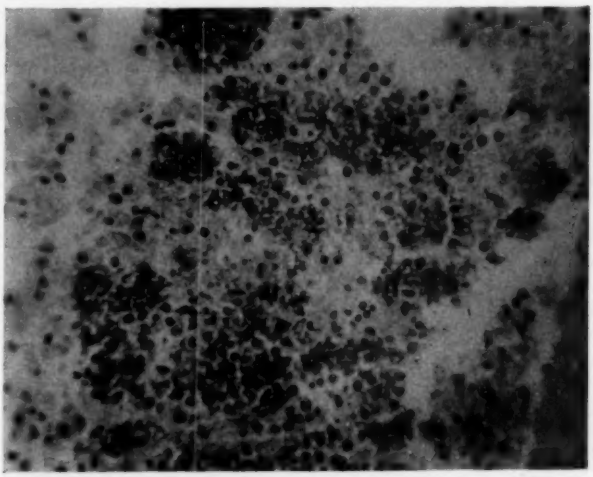


Fig. 6 (Case 2).—Photomicrograph of the lung (high power). Note masses of staphylococci in center of abscess.

CASE 3.—V. L. P. (No.A-41616), a white female, 8 weeks of age, was admitted to Grady Hospital Oct. 3, 1940, with infectious diarrhea of one day's duration. *B. dysenteriae* Shiga was cultured from her stools. The infant was treated with sulfathiazole and made a good recovery. She remained well nourished throughout her hospital stay. When about to be discharged she contracted an upper respiratory infection which became progressively worse. On Oct. 24 the physical examination revealed what appeared to be a beginning pneumonia in both lung fields. The patient was obviously acutely ill; her abdomen was distended and she was markedly dyspneic. The temperature was 104.5°. Sulfathiazole therapy was resumed and a blood transfusion given.

Laboratory Examination.—On admission the white blood count was 23,000 with 56 per cent polymorphonuclear leucocytes; the red blood count was 3,400,000; hemoglobin, 10.6 Gm. (67.9 per cent). A culture of the sputum showed *Staph. albus;* no pneumococci were cultured.

Course.—On Oct. 28 the patient's condition became worse. A roentgenogram disclosed a lobar consolidation in the right middle lung field and a coarse mottled infiltration of the left lung base. The following morning (Oct. 29) a thoracentesis was performed. After 17 c.c. of thick brownish fluid had been aspirated, 5 gr. of sulfathiazole in 5 c.c. of sterile physiologic saline were injected into the right pleural cavity. Sulfathiazole was also continued by mouth. A smear made from the pus obtained by aspiration revealed many gram-positive cocci in clumps resembling staphylococci morphologically. Cultures from the same material showed hemolytic *Staph. aureus.* Five thousand units of staphylococcus antitoxin* were given subcutaneously every three hours for five doses, followed by 5 c.c. every four

*Lederle Laboratories.

hours for four doses. The temperature dropped gradually to normal after this treatment. The physical condition of the patient, however, was not comparable to the drop of the temperature. Her color was poor and she became cyanotic as soon as she was taken out of the oxygen tent.

The impression was that the patient had a bilateral staphylococcic pneumonia with formation of multiple abscesses in the lungs. The patient's condition took an unfavorable course and she died Nov. 4. Permission for autopsy was not obtained.

CASE 4.—A. H. (No. 121219), a colored male infant, 2 years old, was admitted to Grady Hospital Jan. 5, 1941, because of cough and rapid respiration for the preceding three days. On the day prior to admission he was noted to have fever, malaise, and abdominal pain. Two weeks before admission he had burned his leg; this wound was healing and was not infected. Physical examination revealed that the patient was acutely ill with a temperature of 102°, a pulse rate of 130, and marked dyspnea. Flaring of the nostrils and moist-sounding coughs were noted. The x-ray examination (Fig. 7) revealed a diffuse homogeneous density in the right middle lung field. The apex of the right lung and the right costophrenic angle appeared clear. There was an increase of the bronchovascular markings noted in the left lung field.

Fig. 7 (Case 4).—Jan. 5, 1941, date of admission; lobar consolidation in right middle lung field.

Laboratory Examination.—The white blood count on admission was 35,000 with 76 per cent polymorphonuclear leucocytes; the red blood count was 4,900,000 with 99 per cent hemoglobin. The urine was negative except for 3 to 5 pus cells per high power field. An intradermal test with 0.1 c.c. of 1:1,000 O.T. was negative in forty-eight hours. The Kahn test was negative.

Course.—The patient received sulfapyridine but failed to respond to this treatment. Three days after admission another roentgenogram was taken (Fig. 8). The diffuse density previously described was still present, but in addition to that about 30 per cent pneumothorax was seen. Pleural adhesions were noted in the right upper lung field, apparently preventing complete collapse of the lung. Fol-

lowing the x-ray examination a chest tap revealed air but no fluid in the pleural cavity. Two days later a third roentgenogram disclosed a hydropneumothorax with numerous adhesions and shifting of the heart to the left side. There appeared a number of cystic areas in the right lung field which were interpreted as either abscess formations within the partially collapsed lung or areas of encapsulated fluid or air in the pleural cavity.

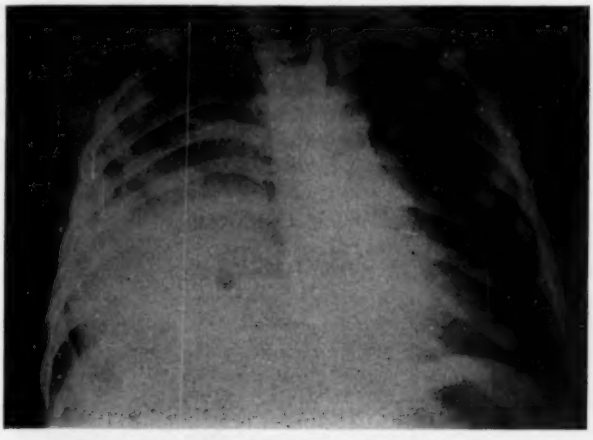


Fig. 8 (Case 4).—Jan. 8, 1941, three days after admission; pneumothorax on right side; free air in apical area.

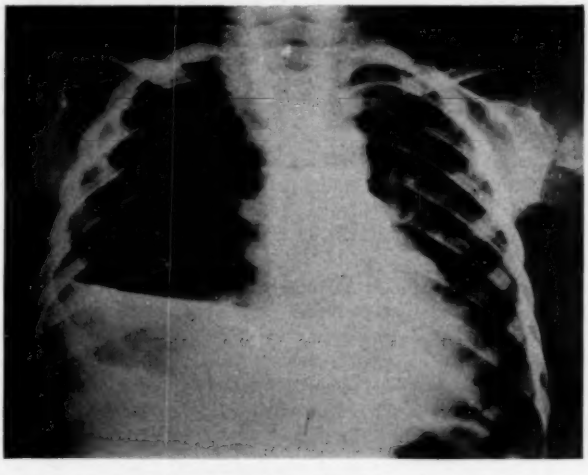


Fig. 9 (Case 4).—Jan. 16, 1941, eleven days after admission; pneumothorax on right side; two fluid levels indicate encapsulated fluid.

Film studies Jan. 16 (Fig. 9) showed two fluid levels in the right hemithorax. On Jan. 22 a closed drainage was performed and 300 c.c. of thick yellow pus was obtained. A culture of this pus revealed *Staph. aureus*.

The condition of the patient improved for a few days. He became acutely ill again with marked increase of temperature and pulse rate. On Feb. 4 a rib resection was done. The patient responded unfavorably and died twelve hours after operation.

Autopsy.—

Essential Gross Findings: The mediastinum was shifted to the left side. The pericardial sac contained some brownish, cloudy fluid and some unorganized fibrinous material. The myocardium and endocardium appeared grossly normal. The left lung appeared retracted toward the mediastinum, but complete collapse of this lung was prevented by several rather dense adhesions which appeared on the lateral and apical aspect of the left upper lobe. Cut section throughout the lung revealed two small abscess cavities in the right middle lobe, measuring about 1 cm. in diameter and filled with yellowish pus. One of these cavities was in direct communication with a funnel-shaped fistula, which extended from the surface of the lung into the parenchyma of the right middle lobe. By injection of water into the trachea this fistula was found in communication with the bronchial tree.

Microscopic Examination: Sections through the wall of the abscesses revealed destruction of the alveolar septa with the appearance of an inflammatory exudate consisting of polymorphonuclear leucocytes, mononuclear cells, and a number of plasma cells. Sections through other portions of the lung showed groups of alveoli filled with red blood cells, polymorphonuclear cells, and large mononuclear cells. There was an inflammatory exudate observed in the bronchi. Masses of cocci resembling staphylococci morphologically were found in the abscess wall.

CASE 5.—V. P. (No. A-51249), a white female child, 1 year old, was admitted to Grady Hospital Jan. 20, 1941, with history of fever, rapid respiration, and cough, with no change in her condition for the preceding five days. On admission the temperature was 103.5°, pulse rate, 180, and respiration, 40. The patient was acutely ill and breathed rapidly in short gasps; the abdomen was markedly distended. A chest examination revealed what appeared to be a massive consolidation of the right lung, and a roentgenogram disclosed a diffuse density throughout the entire right hemithorax with the exception of a small area near the upper mediastinum. The heart showed a little shifting to the left side. The appearance was more that of fluid in the pleural cavity.

The *laboratory examination* showed a white blood count of 31,000 with 70 per cent polymorphonuclear leucocytes; the red blood count was 4,650,000; hemoglobin, 65 per cent. Urinalysis on admission revealed 2 plus albumin with an occasional red blood cell and 3 to 4 pus cells on microscopic examination. A blood culture was negative.

Course.—Because the clinical findings were not in agreement with the x-ray findings, a chest tap was not performed until January 23, when 20 c.c. of thick creamy pus were aspirated from the right chest. Smears from this pus revealed small gram-positive cocci in groups, and a culture showed hemolytic *Staph. aureus.* Treatment consisted of sulfapyridine alternated with sulfathiazole, blood transfusions, and subcutaneous fluids. The child did not respond to this treatment and remained in a toxic condition. She died four days after admission to the hospital. An autopsy was not obtained.

CASE 6.—M. H. P. (No. A-40105), a white female infant, 8 months of age, was admitted to the otolaryngologic service of Grady Hospital Feb. 17, 1941, because of acute right mastoiditis and right subperiosteal abscess. A simple right mastoidectomy was performed on the day of admission. After a hospital stay of eleven days the patient was discharged as well. On March 21, 1941, she was readmitted to the

same service with the diagnosis of right postauricular lymphadenitis. The treatment was conservative, and the swelling of the lymph nodes soon disappeared.

On April 5 she returned to the otolaryngologic department. She had been well until two days previously, when she became suddenly ill with fever, cough, and rapid respiration. A bulging of the eardrum was noted on the left side, and a myringotomy was performed, but there was no pus obtained. The next day the patient was transferred to the pediatric service because it was thought that the chest pathology was the predominant feature of her illness. The physical examination revealed an acutely and seriously ill infant who was breathing rapidly and with difficulty. The skin color was pale and cyanosis was present. There was some bloody discharge from the right ear and a small amount of yellowish discharge from the left ear. Numerous crepitant râles were heard throughout the entire right chest, and there were physical signs of consolidation in the right lung base. The temperature was 105°, the pulse rate, 160, the respiration, 40.

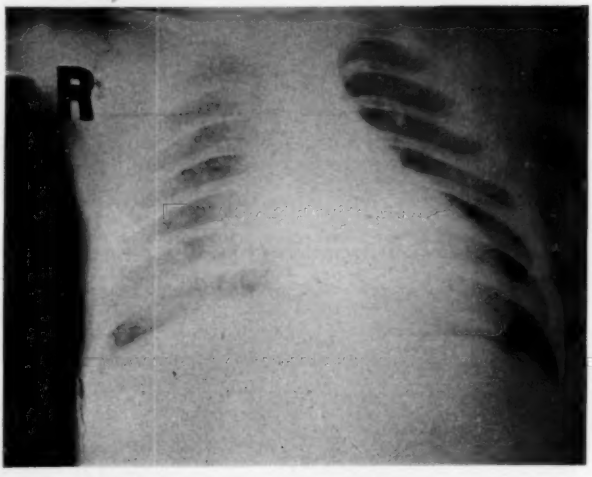


Fig. 10 (Case 6).—April 5, 1941, date of admission; area of consolidation in right lower lung field.

Laboratory examination revealed a white blood count of 14,500 with 70 per cent polymorphonuclear leucocytes; the red blood count was 3,800,000, and the hemoglobin, 60.5 per cent. The urine was negative. An intradermal test with 0.1 c.c. of purified protein derivative, second strength, was negative after seventy-two hours. A roentgenogram (Fig. 10) on the day of admission disclosed a diffuse density throughout the right lung base, having the appearance of a consolidation. The remainder of the lung field appeared clear.

Course.—The infant was treated with sulfathiazole and sulfapyridine; she received blood transfusions and subcutaneous fluids but did not respond to this treatment. Four days after admission a second roentgenogram (Fig. 11) revealed a right hydropneumothorax. There was partial collapse of the right lung. The pleura on the right side was greatly thickened, and adhesions in the region of the right apex were noted. The heart was shifted to the left side. The white blood count had now increased to 37,100 with 74 per cent polymorphonuclear leucocytes. A thoracentesis

was done on April 9 and a small amount of yellow pus was aspirated. A smear from this material revealed gram-positive cocci resembling staphylococci morphologically. *Staph. aureus* was cultured in pure form from the same material. During one attempt at thoracentesis enough air was encountered in the chest cavity to push the

Fig. 11 (Case 6).—April 9, 1941, four days after admission; right pneumothorax; partial collapse of right lung. Roentgenogram taken in supine position; no fluid level.

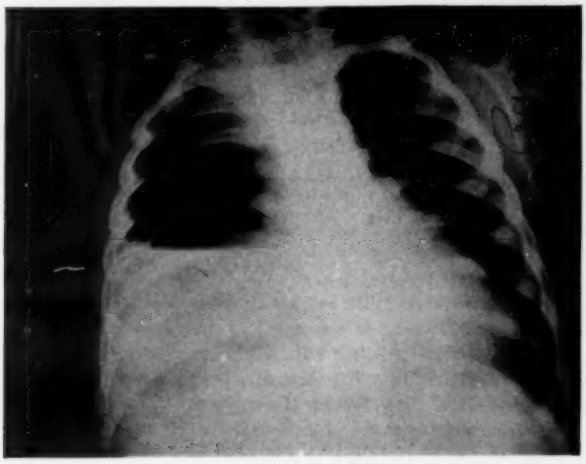


Fig. 12 (Case 6).—April 11, 1941, six days after admission; right hydropneumothorax. Note horizontal fluid level. Roentgenogram taken in erect position.

plunger of the syringe out of the barrel. Subcutaneous emphysema followed the thoracentesis at the site of the aspiration. Subsequent chest taps on following days revealed a change in the color of the chest fluid from yellow to dark reddish brown. Further x-ray study (Fig. 12) demonstrated progressive collapse of the lung with

some encapsulation of fluid. A closed drainage was attempted but was not successful. The patient died after a hospital stay of ten days. Permission for autopsy was not obtained.

COMMENT

Clinical Course.—A sudden onset with high fever, rapid respiration, and cough was observed in all cases. From the onset the patients had a toxic appearance which was maintained throughout the entire course of the illness and was characterized by cyanosis, paleness, and rapid cardiac and respiratory rate. Stupor and unconsciousness were noted in the terminal stages. Meningismus was present in two cases. Abdominal distention was a characteristic finding and occurred early in the disease. The temperature of the patient did not necessarily correspond to the severe clinical picture, since a drop of the temperature was not always followed by an improvement in the patient's condition. In Cases 1 and 2 the temperature returned to normal before the patients died. Convulsions did not occur in any of our cases.

Pneumopyothorax.—The most striking feature in four of the cases was the development of a pneumopyothorax. The pneumopyothorax in these cases occurred before any diagnostic or therapeutic thoracentesis was performed. The pathologic-physiologic basis of this event was the formation of a bronchopleural fistula which developed as a result of the rupture of an abscess and which further contributed to the infection of the pleural cavity.

The development of pneumopyothorax was observed very early in the disease. In Case 2, for instance, the chest roentgenogram presented a normal picture on the day of admission (Fig. 3). The next day a consolidation with possible pleural effusion was noted (Fig. 4), and two days later a pneumothorax with a moderate amount of fluid was demonstrated (Figs. 5*A* and 5*B*). In Case 4 it occurred before the third day and in Cases 1 and 6, before the fourth hospital day.

The physical diagnosis of pneumopyothorax in these very young patients is extremely difficult. The sudden turn for the worse, as indicated by cyanosis, hyperpyrexia, increase of cardiac and respiratory rates, and vomiting of dark brown material, however, should call the attention of the physician to the occurrence of such a complication.

Empyema.—Empyema complicated all of our cases. This complication occurred very early after or simultaneous with the consolidation of the lung. The exudate changed in color, in most cases rapidly, from yellow to dark reddish brown. The cause for this change was hemorrhage into the pleural cavity, originating in all probability at the site of tissue destruction in the abscess cavity. In three of our cases the empyema fluid remained thin during the course of the disease. Staphylococci in large numbers were found in the empyema fluid in all cases.

Bacteriology.—Bacteriologic studies of the pleural exudate were performed in all cases. Gram-positive cocci in groups resembling staphylo-

cocci morphologically were seen on primary smears, and pure colonies of *Staph. aureus* were grown on culture media. In several cases repeated aspirations of pleural fluid were performed. Subsequent smears and cultures confirmed the first reports, which for a while were considered incorrect due to a possible contamination with *Staph. aureus*. We wish to emphasize that the occurrence of *Staph. aureus* in empyema fluid should always be considered a finding of great diagnostic and prognostic significance.

Two infants of our series were first cousins and lived in the same house. Both became ill and died within three months. A carrier, bearing virulent staphylococci, may have been the common source of their infection.

Pathology.—Abscess formation in the lungs was a common feature in all three cases which came to autopsy. The centers of the abscesses contained necrotic material and frequently dense masses of staphylococci (Figs. 2*A* and 6). The remainder of the lung parenchyma showed a tendency to localized suppuration. In these cases an inflammatory exudate, consisting of neutrophiles, large mononuclear cells, and a small amount of fibrin, was found in the alveoli. The interstitial tissue revealed inflammatory reaction. Some of the alveoli were filled with red blood cells, indicating intra-alveolar hemorrhage. The septa were destroyed in the areas of abscess formation.

Complete collapse due to the occurrence of pneumothorax was prevented by the formation of adhesions between the parietal and visceral pleura. These adhesions make the pathologic-anatomic diagnosis of this complication difficult, since they may counteract the shifting of the mediastinum and downward displacement of the diaphragm on the affected side. Unless the chest cavities are opened under water, the pneumothorax may remain undiagnosed.

Roentgenology.—Roentgenologic studies are of the greatest value in the early diagnosis of pneumothorax and pneumopyothorax. Only repeated studies during the disease may reveal these complications. In none of our patients was a pneumothorax present on the day of admission; however in four patients it developed early during the hospital stay. Roentgenograms taken in the supine position, a technique frequently used with ill infants, may obscure the diagnosis, whereas a picture taken in the upright position will clearly demonstrate air in the peripheral portion of the affected chest cavity and will also clearly demonstrate horizontal fluid levels. (Compare Figs. 5*A* and 5*B*.)

Treatment.—The therapy employed in these cases included chemotherapy, staphylococcus antitoxin, surgical procedures, and blood transfusions. The fluid balance was maintained by intravenous and subcutaneous administration of glucose in saline and Hartmann's solution. Food intake was maintained by mouth as long as the patient was conscious.

Sulfamethylthiazole, sulfathiazole, and sulfapyridine were given at a rate of 1.5 to 3 gr. per pound of body weight. When the patient was unable to retain the drug by mouth, the dose was doubled and given per rectum with a retention catheter. In four cases sulfapyridine was given along with sulfathiazole, one drug being administered by mouth, the other by rectum. In one instance sulfathiazole was injected into the pleural cavity. In spite of the early use of these drugs the disease progressed rapidly to a fatal termination. Due to lack of sterile powder of sulfamethylthiazole, sulfapyridine, and sulfathiazole, we did not use the intravenous method of administration. However, we believe that such a method may be of value in the treatment of this highly fatal disease.

Staphylococcus antitoxin used in one patient was followed by a drop of temperature of short duration, but other signs and symptoms were unchanged.

In all patients thoracentesis was performed as a diagnostic and therapeutic procedure. Withdrawal of air resulted frequently in temporary relief from the respiratory distress. On account of the formation of adhesions in the pleural cavity, pus pockets were encountered which frequently did not permit the complete withdrawal of the empyema fluid. In two patients a closed drainage was attempted but was unsuccessful. The results of the attempts might have been more favorable had they been done earlier, before the formation of adhesions which facilitated retention of pus. In one case a rib resection was performed, but the patient died twelve hours after the operation.

Cause of Death.—All of our cases ended fatally. The cause of death seemed to be an overwhelming toxemia. The change of the intrathoracic pressure appeared to play an important role in the patients who developed pneumothorax as a complication. It was frequently observed in these cases that on aspiration of the chest the plunger of the syringe was expelled because of the tension in the pleural cavity. We believe that these pressure changes and their effect upon the respiratory and circulatory systems were responsible, to a great extent, for the unfavorable course of the disease.

SUMMARY

1. Six cases of staphylococcic pneumonia in infants are reported.

2. Pneumopyothorax was a complication in four cases. It occurred before any diagnostic or therapeutic thoracentesis was performed.

3. Early empyema occurred in all cases.

4. Frequent roentgenologic examinations are the most valuable aid in early diagnosis of these complications. The importance of film studies in the erect position is stressed.

5. The clinical, therapeutic, and pathologic aspects of this highly fatal disease are discussed.

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AN OUTBREAK OF TUBERCULOSIS IN INFANTS DUE TO HOSPITAL INFECTION

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THE infection of infants and children from tuberculous nursemaids or other household employees has been frequently recognized and in some communities has led to organized attempts by pediatricians to secure routine examinations of all housemaids as a condition of employment. A situation of even more serious potentialities is the infection of infants or children in hospital wards by a nurse with open but unrecognized pulmonary tuberculosis. On account of the seriousness and the possible legal implications of such multiple infections and the infrequency of their recognition, it seems worth while to record a recent hospital outbreak of tuberculosis resulting from exposure of infants on the maternity ward of a general hospital to a nurse with open tuberculosis.

At the end of January, 1940, the attention of the Department of Public Health was called to two cases of miliary tuberculosis in infants in a small city near Boston. Since disseminated tuberculosis in children is now a rare condition in Massachusetts, the attending physician at once attempted to locate the source of infection. Roentgenologic examination of all members of the two families proved negative as did similar examination of the attending physician and of the milk man, both of whom were common to the two families. The milk supply proved to be adequately pasteurized.

Because both infants were delivered in the same hospital within a month of each other, the investigation next turned to the hospital personnel who had been in direct contact with the babies. Routine x-ray examination of the nursing staff, including two nurses formerly on the obstetrical service who had then left the hospital, showed that one of the regular night nurses had an infiltrative process of the right upper lobe, characteristic of pulmonary tuberculosis, and her sputum was found to contain tubercle bacilli. X-rays of the other nurses proved negative.

This nurse had been employed at the hospital since March 15, 1939, and her duties included all care of infants in the nursery from 11 P.M. to 7 A.M. She gave all night feedings but did not prepare the formulas. Hospital regulations required that she wear a mask and gown for all nursery duty. Her history showed that at the beginning of her training in 1936 she had had an x-ray of the chest which was reported negative. She had not been re-examined till the present time. Although she denied any recent illness, she admitted she had had a cough for the past six months.

From the Massachusetts Department of Public Health, Division of Tuberculosis.

Investigation showed that pasteurized certified milk had been used in the preparation of all formulas given on this ward during the period in question.

In view of the possibility of widespread infection of the infants cared for in this hospital during the period the nurse might have been excreting tubercle bacilli, arrangements were at once made with the hospital authorities and the local board of health for the examination of as many as possible of the infants delivered between March 1, 1939, and January 30, 1940. The parents of such babies were requested by the hospital to bring them in to clinics to be held at specified hours at the hospital, and the examinations were made during February and March, 1940. At the first visit an intracutaneous tuberculin test was performed, using 0.01 mg. of old tuberculin. The tests were read on the second visit forty-eight hours later and the children who failed to react were retested with 1.0 mg. Approximately 100 tests were made by a pediatrician on the hospital staff. An x-ray of the chest of all reactors was made. The results of the tuberculin test are given in Table I.

TABLE I

TUBERCULIN REACTIONS AMONG INFANTS EXPOSED TO TUBERCULOSIS INFECTION IN A HOSPITAL NURSERY

Total infants delivered in hospital March 1, 1939, to January 30, 1940	506
Total infants tested (February and March, 1940)	426
Total reactors to Mantoux Test*	26
Percentage of reactors among infants tested	6.1

*Including two babies who died of miliary tuberculosis.

TABLE II

INCIDENCE OF REACTORS BY MONTH OF BIRTH

MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN.	TOTAL
5	1	1	4	0	5	5	1	0	4	0	26

Although a certain number of infants in the general population would be expected to react to the tuberculin test at a mean age of 8 months, the reaction rate obtained in this group, 6.1 per cent, is three times the rate found among children tested in Massachusetts Well Baby Clinics, at a mean age of 2½ years. It should be added that of the 506 babies born in the hospital during this period, 12 had died of causes other than tuberculosis, as confirmed by the death certificates, in addition to the 2 who died of miliary tuberculosis.

To get an idea as to whether the infection of infants at this hospital took place at any particular time, the reactors were tabulated by month of birth. There is of course no way of determining which babies acquired their infection while in hospital, but Table II suggests that infection may have been taking place there rather continuously during the period in question.

Of the twenty-six infants who reacted to the tuberculin test, seven showed roentgenologic evidence of tuberculosis. Two, as previously stated, died of miliary tuberculosis and the diagnosis was confirmed by autopsy. Two more of these reactors were subsequently admitted to the Children's Hospital, Boston, the first in April, 1940, with a diagnosis of pulmonary tuberculosis, and the second in August with a diagnosis of tuberculous tracheobronchial nodes with atelectasis. Both recovered. The remaining three infants showed tracheobronchial lymph node enlargement characteristic of tuberculosis but have not developed symptoms of disease.

To rule out the possibility of familial infection, as many as possible of the contacts of the reacting infants were x-rayed. Examinations were completed on all members of seven families, but no cases of active tuberculosis were found. The attempt was made to follow all reacting infants with periodic roentgenograms and to retest all negative reactors born in the hospital between November 1, 1939, and January 30, 1940, when the infectious nurse was removed from the nursery. Lack of interest on the part of parents has made it impossible to secure any considerable number of retests, and only ten of the reacting children were brought in for x-ray in March, 1941. At that time none showed any evidence of pulmonary disease.

COMMENT

A epidemiologic outline is presented of an outbreak of tuberculosis in infants, traceable to exposure to a nurse with open tuberculosis in a hospital nursery. Although recognition of the excess incidence of tuberculosis in student nurses and medical students has resulted in special examinations and regulations for the protection of these groups in most of the better hospitals, little consideration has been given to the possibility of the infection of patients by tuberculous personnel. In view of the experience cited, it is obvious that the examination of nurses should not stop with the completion of training and that the prevention of tuberculous infection of infants in the hospital is a definite responsibility of the administrator, the obstetrician, and the pediatrician.

The examination of nurses for tuberculosis, for the protection of their own health and that of their patients, should start with an intracutaneous tuberculin test and an x-ray of the chest at the beginning of training. Negative reactors should be retested every six months and kept under close observation for approximately two years after this test becomes positive, and all student nurses x-rayed at least once a year, and upon the development of any symptoms suggestive of respiratory disease. On obstetrical wards and in nurseries, especially, all nurses and attendants who come in contact with patients should have regular radiographic examination of the chest annually and also upon any special indication. Strict medical asepsis is of course essential in the

operation of nurseries, but this should not be allowed to take the place of proper examination of the nurse herself, nor does it afford her the protection to which she is entitled.

From the clinical standpoint this experience emphasizes two points: (a) that babies can be infected with tuberculosis during the earliest days of life, and (b) that such infections in certain cases tend to progress rapidly and often result fatally.

Finally, the diagnosis of tuberculous meningitis or of generalized tuberculosis in an infant or child should be the signal for an immediate, intensive search for the source of infection. On account of the great reduction in the general incidence of tuberculosis during the past forty years, such massive infection in an infant or young child almost invariably points to an open case of tuberculosis in the family or among other immediate associates. The prevention of further infection as well as treatment of the initial case must always be kept in mind.

PERTUSSIS TREATED WITH PERTUSSIS ANTIGEN

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IN EARLY March of 1940 coughing was reported among a group of children at the Summit County Children's Home. These children occupied one department of the home and varied in age from 3 to 9 years. The cough we heard was not the typical paroxysm of pertussis, yet the number of children involved made us suspicious that pertussis might be in the offing. With this in mind we began recording the coughing spells. This record we hoped would enable us to demonstrate the beneficial results of therapy we planned to establish when the disease could be diagnosed clinically. We withheld therapy until the typical paroxysms appeared in order to make our study apply to the physician in private practice, who, in the majority of instances, cannot arrive at a positive diagnosis until he has heard or has had described for him the typical paroxysmal cough.

The thirty-six children under observation in our study lived together in one department the entire seven weeks of observation. They were all fed in the same refectory, played together indoors and out-of-doors, and slept in the same dormitory. Nurses were in attendance day and night and carried a chart with them while on duty, marking a vertical line after the child's name every time he had a coughing spell. At first we varied the length of the line to correspond to the severity of the coughing spell. Later, as the paroxysms became more severe, we found this could not be done with any great degree of accuracy; therefore, one vertical line was used to denote either a mild or severe coughing spell.

After twelve days' observation there was no doubt as to the diagnosis of pertussis. The coughing spells were prolonged and in some instances were followed by a breath-holding period or an occasional inspiratory crow. This condition was present in the majority of the children. As this is about the time the average case of pertussis is diagnosed in the private home, one is justified in supposing that any therapeutic agent offered as a cure for pertussis should be effective during this period of the disease. Fortunately not all of the patients had advanced to the stage where a clinical diagnosis could be made. Some of them were just beginning to cough so that we had the added advantage of seeing the results of therapy administered early.

For the purposes of our study the 36 children were divided into three groups. Group 1 received the treatment and Group 2 of equal size was used as a control, while Group 3 contained the children who had the disease before. In the beginning Groups 1 and 2 were of equal size, and, as nearly as possible, contained children of equal age and in the same stage of coughing. Further investigation by our social

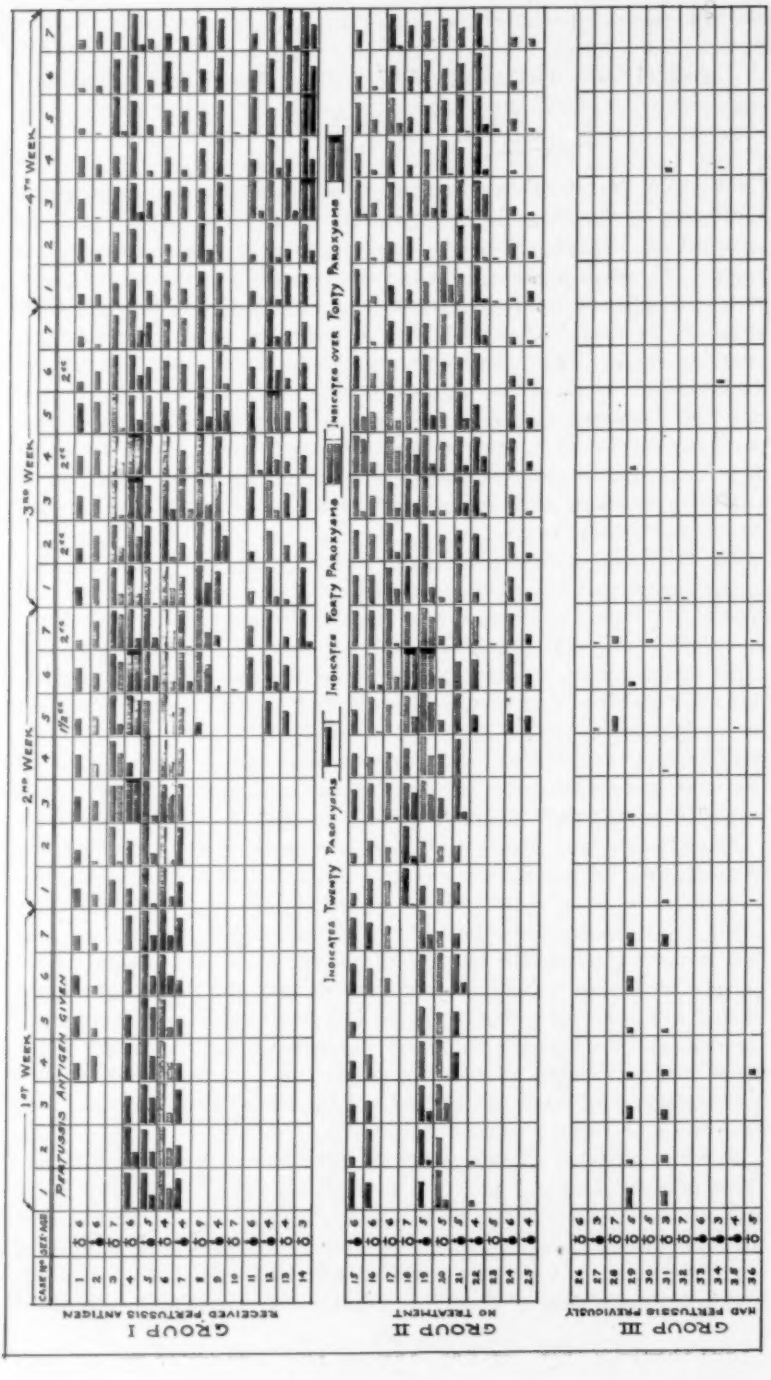
GROUP I
RECEIVED PERTUSSIS ANTIGEN
GROUP II
NO TREATMENT
GROUP III
HAD PERTUSSIS PREVIOUSLY
1ST WEEK
2ND WEEK
3RD WEEK
4TH WEEK
PERTUSSIS ANTIGEN GIVEN
INDICATES TWENTY PAROXYSMS
INDICATES FORTY PAROXYSMS
INDICATES OVER FORTY PAROXYSMS

Chart 1.

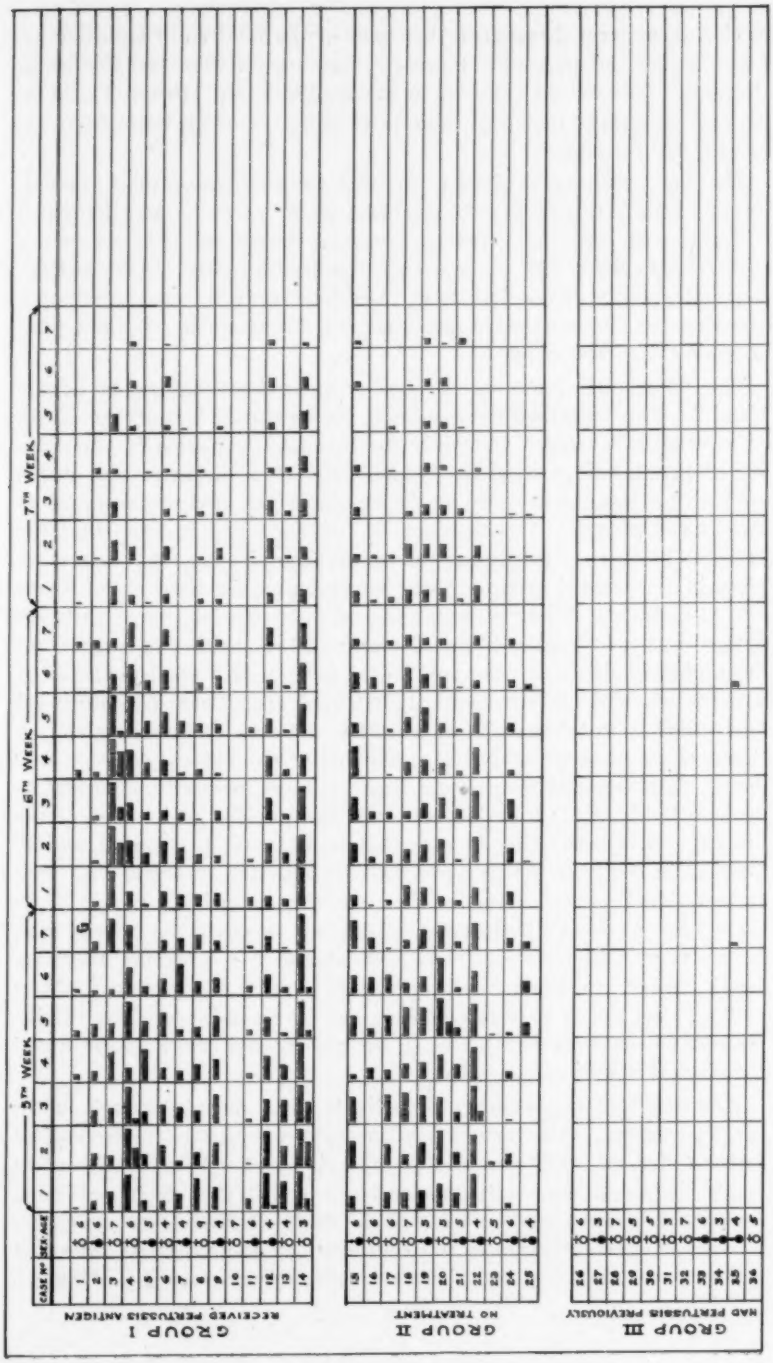
GROUP I
RECEIVED PERTUSSIS ANTIGEN
GROUP II
NO TREATMENT
GROUP III
HAD PERTUSSIS PREVIOUSLY
5TH WEEK
6TH WEEK
7TH WEEK
CASE No
SEX
AGE

Chart 2.

service department determined that some of the children in both Groups 1 and 2 had had pertussis; therefore their names were transferred to Group 3. This left 14 children in the treated group (Group 1), 11 in the control group (Group 2), and 11 in Group 3, or all those who previously had pertussis.

The therapeutic agent given to Group 1 was pertussis antigen (detoxified).* This is a toxic filtrate produced by *H. pertussis* and detoxified with formalin. Adequate curative dosage as recommended by the manufacturer was used; 1½ c.c. were given subcutaneously on the twelfth day of the study as the first dose; then 2 c.c. were injected at two-day intervals for four successive doses, making five doses in all for a total of 9½ c.c. for each child.

The course of the study which lasted seven weeks is pictured on Charts 1 and 2. This visualizes the results of the treatment better than it can be expressed in words. Certainly there was no reduction in the number of paroxysms of coughing immediately after the injections of the antigen nor was the severity or the length of the disease influenced in the treated groups. A comparison of Groups 1 and 2 shows that the patients in the control group ran approximately the same course as those in the treated group. Some benefit might be claimed for Cases 8 to 14 inclusive. These patients received the five injections of pertussis antigen at the beginning of the disease, and the disease ran a course of five and one-half weeks compared to the seven-week period in the other patients who did not receive treatment until the disease had advanced twelve days. But this claim of benefit is not valid because control patients, Cases 22 to 25, inclusive, ran a similar abbreviated course. Evidently those patients who have a slight relative immunity, sufficient to prolong the incubation period, also will have a shortened course of the disease. It is interesting to note that in Case 10 in Group 1 and in Case 23 in Group 2 the patients went through the epidemic with only an occasional coughing spell. The children comprising Group 3, or those who previously had pertussis, did not contract the disease even in the very mild form that was encountered in a previous whooping cough study.[1] Certainly the charts do not reveal any beneficial effects of the injections of pertussis antigen, whether administered at the beginning of coughing or later when the paroxysmal cough develops and the clinical diagnosis is evident.

Knowing that the majority of patients with whooping cough in the early paroxysmal stage manifest a leucocytosis with relative increase of lymphocytes, we might expect a therapeutic agent with a curative effect on the disease to accentuate, accelerate, or modify this response. Therefore beginning on the seventh day of the study we made leucocyte counts as well as differential white cell counts on all the children. The first counts were taken five days before treatment was started in Group 1

*Lederle Laboratories.

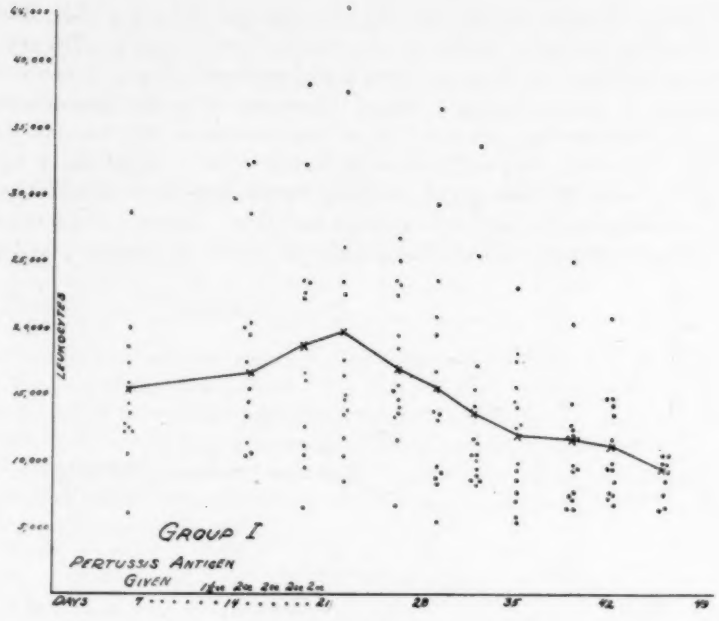

Chart 3.

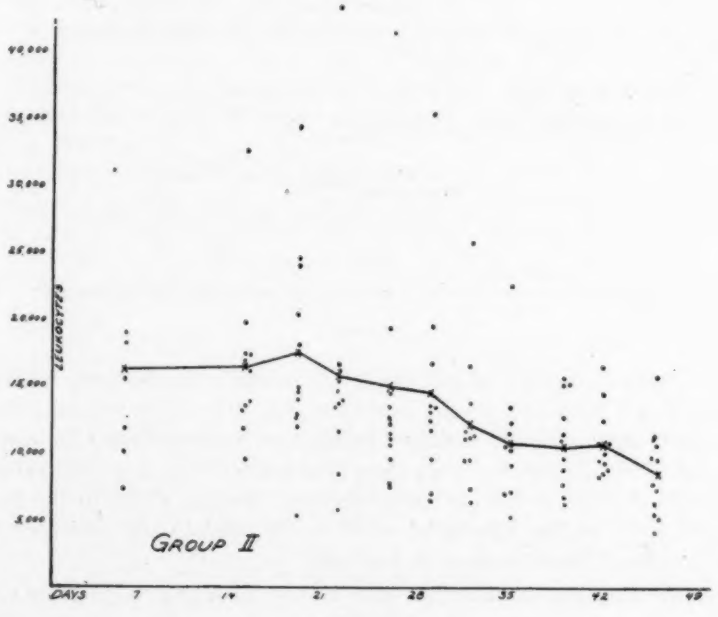

Chart 4.

and were continued at three- or four-day intervals for six weeks. The curves of the leucocyte counts can be seen in Charts 3 and 4. The only variation between the treated Group 1 and untreated Group 2 patients occurred on the twenty-first day of the study after the patients in Group 1 had received five doses of pertussis antigen. On this day we found the average leucocyte count of Group 1 to be 3,000 above the control. Certainly this slight variation would have little significance and would be within a normal expected variation. Charts 5 and 6 show the lymphocyte and polymorphonuclear cell counts of Groups 1 and 2

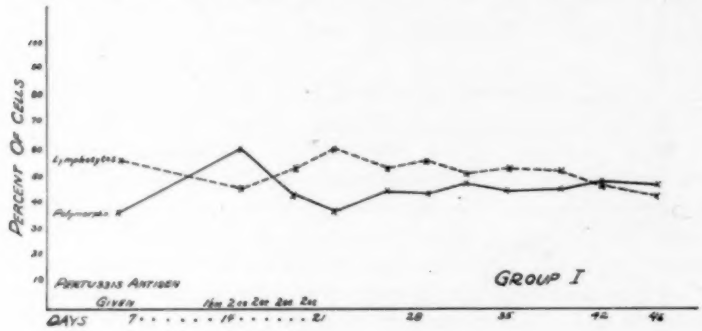

Chart 5.

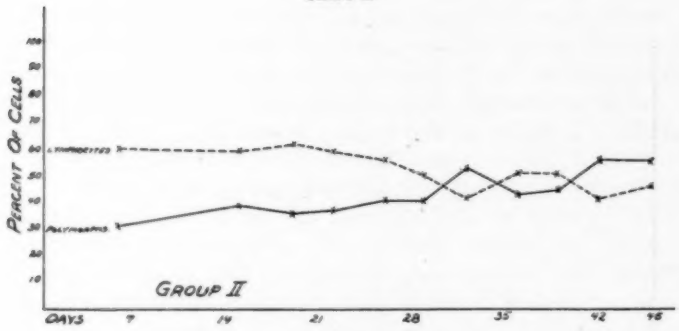

Chart 6.

at the various periods of the study. Here again the variation in the treated and untreated groups is very slight. The untreated patients, Group 2, show a slightly sustained lymphocyte increase during the early period of the disease, but even these counts are within a normal range for well children in the age group studied. Nothing either in the leucocyte count or the differential count would point to any modification of the normal blood response in pertussis.

Many textbooks on pediatrics state that in whooping cough there are many more paroxysms of coughing at night than during the day. To

check this statement the paroxysms were counted during the night period (7 P.M. to 7 A.M.) and compared to the number in the day period (7 A.M. to 7 P.M.). The results are tabulated in Table I and show that about two-thirds of the coughing spells do occur between 7 P.M. and 7 A.M.

TABLE I

	7 A.M. TO 7 P.M. (NUMBER)	7 P.M. TO 7 A.M. (NUMBER)	7 A.M. TO 7 P.M. (%)	7 P.M. TO 7 A.M. (%)
Paroxysms in group 1	2,502	3,878	39.12	60.78
Paroxysms in group 2	1,684	3,029	35.73	64.27
Paroxysms in both groups	4,186	7,007	37.4	62.6

The night period was again broken down into an early period (7 P.M. to 11 P.M.) and a late period (11 P.M. to 7 A.M.). During the earlier period there were 3,329 paroxysms against 3,678 for the later period, about equal numbers in each period. Since the earlier period contained only four hours against eight hours for the later period, we can definitely state that the maximum intensity of coughing in pertussis occurs during the early hours of the night.

CONCLUSIONS

1. Pertussis antigen administered early and at the beginning of the paroxysmal stage of whooping cough did not alleviate the severity of the disease or influence the subsequent course.

2. Pertussis antigen did not modify the blood response in whooping cough.

3. There were more paroxysms of coughing at night than during the day. The first third of the night period is the time of maximum coughing.

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STUDIES OF AMINO ACID ADMINISTRATION

I. Utilization of an Enzymatic Digest of Casein

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BETWEEN 1912 and 1916 several reports appeared in the literature concerning the utilization of amino acids prepared by digestion of casein.[1, 2, 3, 4] Recently, due to the development by the Mead Johnson Laboratories[5, 5a] of a particularly promising casein digest which became available for study, observations concerning its utilization in human beings when administered by both parenteral and oral routes have been reported by Elman,[6] Carbould,[7] Fetzer,[8] Shohl,[9] Farr,[10, 10a] Altshuler,[11] and their co-workers. Still more recently, studies concerning the possible value of such amino acid mixtures in promoting regeneration of plasma protein and in correcting hypoproteinemia have been made by Madden,[12, 13] Holman,[14] and Elman,[15] and their co-workers and by us (unpublished data).

The work to be reported here was undertaken during the summer and fall of 1940 as part of a broad study of parenteral feeding. Its chief purpose was investigation of the possibilities of parenteral administration of the digest and comparison of its utilization when given enterally and parenterally.

METHOD OF STUDY

Nitrogen balance studies were made with the casein digest* given in the following ways: (1) as a supplement to the diet; (2) as a replacement of meat, milk, and eggs in the diet; and (3) as the only appreciable source of nitrogen, given either enterally, intravenously, or by combined enteral and intravenous routes.

Selected children who were in the hospital for long periods were used for the study. During the periods of observation they were allowed about the ward when their condition permitted. Special nurses trained for the work cared for them and prepared the diets. Nitrogen balance studies were made in three-day periods. Usually, except when continuous balances were run, the patients received the particular diets for a period of from two to five days before the balances opened.

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

*This casein digest furnished us as Laboratory Products 92-Z and 92-403, now given the trade name "Amigen," was made through the hydrolytic action of the enzymes of pork pancreas on casein. During hydrolysis, the protein of the pancreas is also digested, so that 85 per cent of the nitrogen in the final product comes from casein and 15 per cent from the pancreas. The dry material contains approximately 12 per cent total nitrogen and 7.4 per cent amino nitrogen. It is stated (personal communication) that guinea pigs cannot be sensitized to it and that it is pyrogen-free.

PREPARATION OF DIETS

The patients were placed on diets which were estimated to be adequate for total metabolic requirements. In some instances it was possible to keep the total calories and the carbohydrate to fat ratios reasonably constant; in others this was not accomplished. Essential vitamins were supplied in the form of commercial preparations. The carbohydrate, fat, and caloric contents of the diets were estimated from the tables of McCance and Widdowson.[16] The nitrogen content of all food fed was determined directly by analysis of duplicate weighed samples which were made into a homogeneous mixture in sulfuric acid by use of a mechanical stirrer.

In certain diets the "nitrogen-free" component was concocted from foods containing only traces of nitrogen, as indicated by the tables, and was then checked by actual analysis. Olive oil and butter were used for fat. Cane sugar, dextrose, lemon juice, and peaches, pears, and apples were sometimes included for carbohydrate. The casein digest was incorporated into the diet in various ways, according to the preferences of the individual subjects. This was accomplished by making up pastes, solutions, or mixtures with other food ingredients and then seasoning with flavorings and condiments. Despite these measures, the combinations sometimes proved distasteful and nauseating; vomiting, however, was exceedingly rare. With some of the diets containing the casein digest which were almost completely without residue, constipation occurred and was remedied with mineral oil. On the other hand, with these same diets diarrhea occasionally occurred and was corrected with paregoric.

The casein digest for intravenous administration was prepared as a 5 per cent solution in freshly distilled water and was then passed with sterile technique in rapid succession through a Seitz, then a Berkefeld filter to remove pyrogens and bacteria. Usually merthiolate was added in final dilution of 1:20,000 to inhibit growth of molds. The solutions for use were diluted so that the final concentration of casein digest was 1 per cent or 2½ per cent with 5 or 10 per cent dextrose. The pH of the 5 per cent solution was usually 4.9. No neutralization was attempted. Intravenous administration was frequently accompanied by nausea, but vomiting usually did not occur if the stomach was empty at the time the injection was started. One 13-year-old girl (A. R.) suffered violent chills followed by sharp rises in temperature when 2½ and 1 per cent solutions were administered intravenously on two different days. The same lot of material caused no reaction in three other children to whom it was given. Repeated injections of either 2½ or 1 per cent solutions sometimes caused phlebitis and thrombosis of veins. Frequently, administration by the continuous drip method resulted in marked edema of the extremity used when the injection lasted as long as two or three days.

COLLECTION OF URINE AND STOOLS

The stools were marked with carmine, and the urine and stools were collected separately. When infants were studied, they were placed on padded canvas metabolism frames. Preservation of urine was accomplished by the addition of 5 c.c. of concentrated sulfuric acid. Stools were placed in sulfuric acid and, before analysis, were made into a homogeneous mixture by the use of an electric stirrer. Vomitus was treated in a similar fashion and its nitrogen content determined and subtracted from the nitrogen intake.

CHEMICAL ANALYSIS

The total nitrogen of the food, urine, and stools was determined by macro-Kjeldahl analysis, using the Arnold Gunning technique with 30 per cent hydrogen peroxide as an extra oxidizing agent.[17] Urine protein nitrogen was estimated by difference after the nonprotein nitrogen had been determined on a tungstic acid filtrate. The chemical analyses were made chiefly by two of us (C. M. and H. G. M.) and nearly all of the determinations were run in triplicate.

CASE REPORTS

CASE 1.—A. J., a 2-year-old colored boy with a lye stricture of the esophagus, was admitted to the hospital for dilatations. His nutrition had been well maintained by gastrostomy tube feeding. The total serum protein was 7.08 Gm. per 100 c.c. and the albumin, 4.19 Gm.

During the first period, on a diet containing 0.44 Gm. nitrogen (2.7 Gm. protein) per kilogram of body weight derived largely from dairy products, the patient was in positive nitrogen balance and retained 0.15 Gm. nitrogen per kilogram per day (Table I). When the protein of this diet was replaced by an amount of casein digest which provided 0.52 Gm. nitrogen per kilogram of body weight, the nitrogen retention was approximately the same, 0.17 Gm. per kilogram. During the third period the nitrogen intake was 0.48 Gm. per kilogram and again was derived largely from casein digest, but one-half was given enterally and one-half intravenously. On the second day the intravenous injection was accompanied by a chill, and the patient's temperature rose to 38.8°. In the fourth period no casein digest was given enterally, but the intravenous injection was continued. The total nitrogen intake was only 0.27 Gm. per kilogram per day, 73 per cent of it being derived from casein digest. On these two days the fever was again high, reaching 40° and 40.3°, respectively, and for this reason the injections were discontinued. It will be noted from Table I that in the period when casein digest was given both enterally and intravenously the nitrogen retention was less than half of that in the preceding period. It is possible that the reduced retention may have been associated with the fever which occurred on the second day, for on this day the urinary nitrogen was considerably increased. In the fourth period the shift to a negative balance was not unexpected, for the nitrogen intake had been reduced by almost 50 per cent without an adjustment period having been allowed, and, in addition, the fever was high. It cannot be said whether the balance would have become positive if the intravenous administration of the indicated amount of casein digest could have been continued without reaction. In the fifth period, when the same amount of casein digest that had been given by vein was given enterally, there was slight nitrogen retention.

TABLE I

CASE 1 A. J. AGE, 2 YEARS STRICTURE OF ESOPHAGUS GASTROSTOMY FEEDINGS

DATE	BODY WEIGHT (KG.)	FOOD INTAKE							NITROGEN			
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	NITROGEN (GM.)				EXCRETION		BALANCE	
					FOOD	CASEIN DIGEST		TOTAL PER KG.	URINE (GM.)	FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
						ENTERALLY	I.V.					
10/14/40	13.1	1,340	170	58	5.45				2.66			
10/15/40		1,340	170	58	5.63				3.32			
10/16/40		1,340	170	58	5.92				3.41			
Average		1,340	170	58	5.66			0.44	3.13	0.58	+1.95	+0.15
10/21/40	11.8	1,354	170	58	0.69	5.40			3.84			
10/22/40		1,354	170	58	0.69	5.40			*3.88(+)			
10/23/40		1,354	170	58	0.69	5.40			4.06			
Average		1,354	170	58	0.69	5.40		0.52	3.93(+)	0.21	+1.95+	+0.17+
10/24/40	12.7	1,380	170	58	0.82	2.70	2.70		4.18			
10/25/40		1,380	170	58	0.82	2.70	2.70		5.59			
Average		1,380	170	58	0.82	2.70	2.70	0.48	4.88	0.54	+0.80	+0.06
10/26/40	12.7	1,416	181	67	0.74		2.70		4.46			
10/27/40		1,416	181	67	0.74		2.70		4.12			
Average		1,416	181	67	0.74		2.70	0.27	4.29	0.21	−1.06	−0.08
10/28/40	12.7	1,380	181	67	0.70	2.70			4.00			
10/29/40		1,380	181	67	0.70	2.70			2.51			
10/30/40		1,380	181	67	0.70	2.70			2.38			
Average		1,380	181	67	0.70	2.70		0.27	2.97	0.15	+0.28	+0.02

*Small amount of urine lost.

Interpretation.—When the usual food protein was replaced by casein digest, the patient remained in positive nitrogen balance and the amount of nitrogen retained was unchanged. When part of the casein digest was given enterally and part intravenously, chills and fever resulted, making difficult interpretation of this part of the data.

CASE 2.—O. S., also a 2-year-old colored boy with a lye stricture of the esophagus, was in the hospital for dilatations. He, too, was fed through a gastrostomy tube. He was otherwise normal physically. The serum protein was 7.29 Gm. per 100 c.c., and the albumin, 4.14.

During the period when a diet containing 0.47 Gm. of nitrogen per kilogram of body weight per day, largely in the form of milk and eggs, was given, and during the period when casein digest in approximately the same amount replaced the usual food protein, the nitrogen retentions were nearly identical, 0.16 and 0.15 Gm. per kilogram per day, respectively (Table II). During the third period in which the quantity of casein digest given was unchanged but one-half was administered enterally and one-half intravenously, the nitrogen retention again was almost the same. This period lasted only two days, because on the second day the child had fever, and it was thought, owing to recent exposure, that he might be developing chicken pox. On Oct. 12, four days later, typical lesions were noted. During the last period, when the child was recovering from chicken pox, the nitrogen intake, which consisted of casein digest given enterally, was approximately one-half of that previously given, and the nitrogen retention also was about half that noted during the first two periods.

Interpretation.—When the usual dietary nitrogen was replaced by nitrogen of enzymatic casein digest, which was given either enterally or by combined enteral and intravenous routes, the patient remained in positive nitrogen balance.

CASE 3.—C. E., a 5-year-old white boy, was admitted to the hospital for tonsillectomy because of recurrent tonsillitis and chronic malnutrition. Except for large infected tonsils, malnutrition, and a mild degree of anemia, he was quite well.

During the first balance period he received each day a total of 103 calories per kilograms of body weight and 0.61 Gm. of nitrogen per kilogram, which was derived from the usual food protein. During this time the nitrogen retention averaged 0.03 Gm. per kilogram per day (Table III). In the next period the nitrogen intake was 0.76 Gm. per kilogram, 68 per cent of which was derived from casein digest and the remainder from fruits and vegetable protein; and the nitrogen retention again was positive, averaging 0.09 Gm. per kilogram per day.

Interpretation.—When animal protein in the diet of a malnourished child was replaced by casein digest, the nitrogen balance remained positive, suggesting that the nitrogen of the casein digest was well utilized.

CASE 4.—O. A., a 2½-year-old white boy, was convalescing from acrodynia which had led to a severe degree of malnutrition. The patient, however, was not anemic and the serum total protein on one occasion was 7.07 Gm. per 100 c.c., with 5.48 Gm. of albumin.

For a period of two weeks after admission the patient was offered the regular ward diet and ate very poorly. During the first nitrogen balance period, which was not preceded by a period of weighed diet, the caloric value of the food offered

TABLE II

CASE 2 O. S. AGE, 2 YEARS STRICTURE OF ESOPHAGUS GASTROSTOMY FEEDINGS

DATE	BODY WEIGHT (KG.)	FOOD INTAKE							NITROGEN			
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	NITROGEN (GM.)				EXCRETION		BALANCE	
					FOOD	CASEIN DIGEST		TOTAL PER KG.	URINE (GM.)	FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
						EN-TERALLY	I.V.					
9/26/40	11.8	1,272	184	44	5.49				2.75			
9/27/40		1,272	184	44	5.56				3.14			
9/28/40		1,272	184	44	5.38				3.06			
Average		1,272	184	44	5.48			0.47	2.98	0.67	+1.83	+0.16
9/30/40		1,282	150	58	0.79	4.8			3.14			
10/ 1/40		1,282	150	58	0.79	4.8			3.13			
10/ 2/40		1,282	150	58	0.79	4.8			3.31			
Average		1,282	150	58	0.79	4.8		0.47	3.19	0.46	+1.84	+0.15
10/ 7/40		1,282	150	58	0.78	2.4	2.54		4.14			
10/ 8/40		1,282	150	58	0.78	2.4	2.54		3.17			
Average		1,282	150	58	0.78	2.4	2.54	0.48	3.65	0.37	+1.72	+0.14
10/14/40		1,278	160	62	0.88	2.4			2.19			
10/15/40		1,278	160	62	0.88	2.4			1.66			
10/16/40		1,278	160	62	0.88	2.4			1.76			
Average		1,278	160	62	0.88	2.4		0.25	1.87	0.34	+1.07	+0.08

TABLE III

CASE 3 C. E. AGE, 5 YEARS MALNUTRITION ASSOCIATED WITH CHRONIC INFECTION

DATE	BODY WEIGHT (KG.)	FOOD INTAKE							NITROGEN			
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	NITROGEN (GM.)				EXCRETION		BALANCE	
					FOOD	CASEIN DIGEST		TOTAL PER KG.	URINE (GM.)	FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
						EN-TERALLY	I.V.					
8/ 8/40	14.5											
8/14/40		1,490	178	62	8.29				7.48			
8/15/40		1,490	178	62	8.84				7.14			
8/16/40		1,490	178	62	9.22				7.46			
Average		1,490	178	62	8.78			0.61	7.39	0.99	+0.40	+0.03
8/20/40	15.0	1,518	197	42	3.68	7.8			9.68			
8/21/40		1,518	197	42	3.97	7.8			8.36			
8/22/40		1,518	197	42	3.45	7.8			7.70			
Average		1,518	197	42	3.70	7.8		0.76	8.65	1.40	+1.45	+0.09

averaged 172 calories per kilogram per day, with 0.65 Gm. of nitrogen per kilogram derived from the usual foods. The diet was not well taken, however, and each day the nitrogen content of the uneaten portion was determined by analysis; the actual nitrogen intake averaged 0.48 Gm. per kilogram per day, and the retention in this period was 0.11 Gm. per kilogram per day. In the second period casein digest was added to the diet so that the average nitrogen intake was 0.89 Gm. per kilogram per day, with approximately one-third of it derived from the casein digest, and the total caloric intake was 157 calories per kilogram. The nitrogen retention was essentially the same.

CASE 5.—A. R., a 12-year-old white girl, was admitted to the hospital on May 6, 1940, because of intractable diarrhea which was found to be due to ulcerative colitis of undetermined origin. She had had the disease for nine months prior to hospitalization and had lost 15 pounds. Physical examination revealed slight enlargement of the liver and the proctoscopic finding of a hyperemic rectal mucosa studded with occasional small ulcers.

The urine was not abnormal. The blood count revealed a slight anemia and a leucocytosis, the white blood cells numbering from 11,000 to 19,000. The serum total protein was 6.68 Gm. per 100 c.c. Stool cultures were negative for organisms of the typhoid and dysentery groups, and examination for parasites also was negative.

The patient was given a low residue, high caloric diet with added commercial vitamin preparations. On May 29 treatment with neoprontosil was started, on June 7 addition of casein digest to the diet was begun, and on June 24 kaopectate was added.

Preceding and during the first nitrogen balance period, the patient received each day approximately 96 calories per kilogram of body weight, with 0.69 Gm. of nitrogen per kilogram, 42 per cent of which was derived from casein digest (80 Gm. of casein digest per day). In addition she was given each day neoprontosil, 6 Gm.; thiamine chloride, 1.5 mg.; nicotinic acid, 200 mg.; Kinney's yeast extract, 8 c.c.; oleum percomorph, 45 drops; kaopectate, 90 c.c.; and ascorbic acid, 100 mg. The nitrogen balance was markedly positive, the retention averaging 0.15 Gm. per kilogram per day. The child's general conditon became considerably improved; and between July 5 and July 23 the number of stools decreased from three to five a day to one or two. The casein digest was then withdrawn and the patient was given a diet containing 0.59 Gm. of nitrogen per kilogram per day, derived from low residue foods. The nitrogen retention was 0.08 Gm. per kilogram per day, and the stool nitrogen did not change appreciably.

The patient continued to do well and returned home on August 4 on a low residue diet without added casein digest. She re-entered the hospital two months later in an acute exacerbation. It seemed advisable to rest the gastrointestinal tract completely, and intravenous feeding with casein digest and glucose was undertaken. On two successive days after having received intravenously some of the same lot of solution used in several other patients without reactions, the child developed chills and fever, which rose to 40° C., and she appeared very much prostrated. No further attempts were made to continue casein digest feeding by vein.

Interpretation.—After several weeks on a low residue diet in which the nitrogen intake was derived chiefly from dairy products and casein digest, the patient who was suffering from chronic ulcerative colitis showed considerable clinical improvement. The nitrogen balance was markedly positive.

TABLE IV

CASE 4 O. A. AGE, 2½ YEARS SEVERE MALNUTRITION (ACRODYNIA)

DATE	BODY WEIGHT (KG.)	FOOD INTAKE								NITROGEN			
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	NITROGEN (GM.)					EXCRETION		BALANCE	
					FOOD		CASEIN DIGEST		TOTAL PER KG.				
							EN-TERALLY	I.V.		URINE (GM.)	FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
		(Of-fered)	(Of-fered)	(Of-fered)	(Of-fered)	(Taken)			(Of-fered) (Taken)				
9/ 4/40	7.2	1,238	99	74	4.57	3.53				2.07			
9/ 5/40		1,238	99	74	4.87	2.63				1.88			
9/ 6/40		1,238	99	74	4.87	4.09				2.50			
Average		1,238	99	74	4.71	3.42			0.65 0.48	2.18	0.42	+0.82	+0.11
		(Taken)	(Taken)	(Taken)		(Taken)	(Taken)		(Taken)				
9/18/40	7.7	1,206	172	37		3.99	2.4			4.75			
9/19/40		1,206	172	37		4.51	2.4			4.16			
9/20/40		1,206	172	37		4.78	2.4			6.66			
Average		1,206	172	37		4.43	2.4		0.89	5.19	0.74	+0.90	+0.12

TABLE V

CASE 5 A. R. AGE, 12 YEARS CHRONIC DIARRHEA ULCERATIVE COLITIS

DATE	BODY WEIGHT (KG.)	FOOD INTAKE							NITROGEN			
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	NITROGEN (GM.)				EXCRETION		BALANCE	
					FOOD	CASEIN DIGEST		TOTAL PER KG.	URINE (GM.)	FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
						EN-TERALLY	I.V.					
7/15/40	31.3	2,989	127	207	11.9	9.6			14.43			
7/16/40		2,989	127	207	12.0	9.6			14.48			
7/17/40		2,989	127	207	12.18	9.6			14.61			
Average		2,989	127	207	12.03	9.6		0.69	14.51	2.30	+4.82	+0.15
7/26/40	33.6	2,898	173	190	19.96				13.96			
7/27/40		2,898	173	190	19.78				15.11			
7/28/40		2,898	173	190	19.86				15.70			
Average		2,898	173	190	19.87			0.59	14.93	2.36	+2.58	+0.08

CASE 6.—R. H., a 6-year-old white girl, entered the hospital on April 14, 1940, with generalized edema, suffering from chronic glomerulonephritis. Five days after entry she developed a type VI pneumococcus peritonitis which was treated successfully with sulfathiazole. In May she had an erysipeloid skin infection which also was treated successfully with the same drug. On several occasions during July and August she developed a mild rhinitis.

The urine on admission contained large amounts of protein; the quantity, however, gradually decreased but with considerable fluctuation from about 12 Gm. per 24 hours to only a trace by qualitative test. Microscopic examination revealed increased numbers of red blood cells, white and epithelial cells, and occasional casts. There was never any appreciable anemia. The blood pressure usually was only slightly elevated and on just one occasion the systolic pressure was noted to be as high as 140 mm. Hg. The blood urea clearance was 155 per cent of the normal. The serum total protein until July remained around 4 Gm. per 100 c.c., and the albumin usually was below 1.5 Gm. With gradual recovery from the nephritis and concomitant with the addition of casein digest to the diet, the total serum protein during the course of three months gradually rose to 6.49 Gm. per 100 c.c., with 3.75 Gm. albumin.

During the first balance period the diet contained the usual food proteins with 0.40 Gm. nitrogen per kilogram of body weight per day, and the nitrogen retention was 0.02 Gm. per kilogram per day (Table VI). In the second period, when casein digest was substituted for the animal protein and comprised about two-thirds of the nitrogen intake with the calories increased about 20 per cent, the nitrogen retained was 0.05 Gm. per kilogram, with, however, some increase in stool nitrogen. In the third period the total caloric intake was again increased and the nitrogen intake was 0.47 Gm. per kilogram and was derived from the usual food. The nitrogen content of the stools decreased considerably, and the retention rose to 0.14 Gm. per kilogram per day. In the fourth period casein digest again replaced the animal protein in the diet but this time constituted slightly less than one-half of the nitrogen intake. Again the stool nitrogen increased but the nitrogen retention was almost the same.

Interpretation.—When casein digest was substituted for animal protein in the diet, the patient continued to have a positive nitrogen balance; there occurred, however, some increase in the stool nitrogen.

CASE 7.—L. B., a 5-year-old colored boy, re-entered the hospital on Sept. 11, 1940, with marked nephrotic edema and an erysipeloid infection of the left knee. He was treated with sulfathiazole, and the infection subsided within a few days. During the time that he was in the hospital and while the nitrogen balance studies were being carried out, the amount of edema varied considerably and occasionally he became edema-free.

On admission there was marked proteinuria and during the period of hospitalization the excretion of protein ranged from less than 1 Gm. per twenty-four hours to 6 Gm. On microscopic examination of the urine, the number of red blood cells did not appear to be increased. There was only a slight degree of anemia. The serum total protein values ranged from 3.08 to 4.77 Gm. per 100 c.c., the albumin from 0.90 to 2.10 Gm., and the nonprotein nitrogen from 20 to 29 mg. per 100 c.c.

Seven nitrogen balance periods were carried out. During the first, the caloric intake was 78 calories per kilogram of ideal body weight (18.6 kg.), with 0.40 Gm. nitrogen per kilogram derived from ordinary foods (Table VII). The nitrogen retention averaged 0.06 Gm. per kilogram per day. In the second period casein digest replaced the usual food protein; the nitrogen intake, being unchanged with the calories, increased to 86 per kilogram. The nitrogen retention was approximately

TABLE VI

CASE 6 R. H. AGE, 6 YEARS NEPHROTIC STAGE OF GLOMERULONEPHRITIS

DATE	BODY WEIGHT (KG.)	FOOD INTAKE							NITROGEN					
					NITROGEN (GM.)				EXCRETION				BALANCE	
						CASEIN DIGEST			URINE					
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	FOOD	ENTERALLY	I.V.	TOTAL PER KG.	TOTAL (GM.)	N.P.N. (GM.)	PROTEIN (GM.)	FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
7/31/40	15.9	1,077	83	65	6.49				5.52	5.13	.39			
8/ 1/40	16.0	1,077	83	65	6.31				5.53	4.50	1.03			
8/ 2/40	16.7	1,077	83	65	6.53				5.44	4.29	1.15			
Average	16.2	1,077	83	65	6.44			0.40	5.50	4.64	.86	0.69	+0.26	+0.02
8/ 5/40	16.2	1,312	123	70	1.81	4.2			4.61	4.50	.11			
8/ 6/40	16.3	1,312	123	70	2.34	4.2			3.81	3.54	.27			
8/ 7/40	16.5	1,312	123	70	1.93	4.2			4.44	3.98	.46			
Average	16.3	1,312	123	70	2.03	4.2		0.39	4.28	4.00	.28	1.08	+0.87	+0.05
8/21/40	16.7	1,642	198	73	8.23				5.59	4.78	.61			
8/22/40	16.6	1,642	198	73	7.86				5.04	4.79	.25			
8/23/40	16.5	1,642	198	73	7.54				5.54	4.75	.79			
Average	16.6	1,642	198	73	7.88			0.47	5.32	4.77	.55	0.27	+2.29	+0.14
9/ 2/40	17.2	1,617	202	65	4.35	3.6			4.40	3.80	.60			
9/ 3/40	17.2	1,617	202	65	4.65	3.6			5.26	4.88	.38			
9/ 4/40	17.1	1,617	202	65	3.64	3.6			4.73	4.70	.03			
Average	17.2	1,617	202	65	4.22	3.6		0.46	4.79	4.46	.33	0.90	+2.13	+0.12

TABLE VII

CASE 7 L. B. AGE, 5 YEARS NEPHROSIS

DATE	BODY WEIGHT (KG.)	FOOD INTAKE							NITROGEN					
					NITROGEN (GM.)				EXCRETION				BALANCE	
						CASEIN DIGEST			URINE					
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	FOOD	ENTERALLY	I.V.	TOTAL PER KG.	TOTAL (GM.)	N.P.N. (GM.)	PROTEIN (GM.)	FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
9/25/40	17.1	1,449	163	68	7.42				6.06	4.75	1.31			
9/26/40	17.4	1,449	163	68	7.49				5.87	5.43	0.44			
9/27/40	17.7	1,449	163	68	7.29				5.94	5.39	0.55			
Average	17.4	1,449	163	68	7.40			0.40	5.95	5.19	0.76	0.42	+1.03	+0.06
9/30/40	19.5	1,595	170	75	0.78	6.40			4.57	4.50	0.07			
10/ 1/40	19.1	1,595	170	75	0.78	6.40			4.75	4.40	0.35			
10/ 2/40	19.1	1,595	170	75	0.78	6.40			4.85	4.47	0.38			
Average	19.4	1,595	170	75	0.78	6.40		0.39	4.76	4.46	0.30	1.06	+1.36	+0.07
10/ 7/40	20.1	1,835	170	75	0.78	13.60			8.21	7.70	0.51			
10/ 8/40	20.2	1,835	170	75	0.78	13.60			10.57	9.49	1.08			
10/ 9/40	20.0	1,835	170	75	0.78	13.60			10.01	8.90	1.11			
Average	20.1	1,835	170	75	0.78	13.60		0.77	9.60	8.70	0.90	1.16	+3.62	+0.19
10/14/40	20.1	1,835	170	75	0.78	13.38			11.95	9.10	2.85			
10/15/40	20.0	1,835	170	75	0.78	13.38			9.85	9.63	0.22			
10/16/40	20.2	1,835	170	75	0.78	13.38			10.40	9.98	0.42			
Average	20.1	1,835	170	75	0.78	13.38		0.76	10.73	9.57	1.16	1.30	+2.13	+0.11
10/21/40	18.2	1,835	170	75	0.78	14.16			11.27	10.70	0.57			
10/22/40	18.2	1,835	170	75	0.78	14.16			*9.81+	9.30+	0.51+			
10/23/40	18.0	1,835	170	75	0.78	14.16			11.25	10.58	0.67			
Average	18.1	1,835	170	75	0.78	14.16		0.80	10.79+	10.19+	0.60+	1.24	+2.91+	+0.16+

*Small amount of urine lost.

TABLE VIII

CASE 8 R. B. AGE, 2½ YEARS NEPHROTIC STAGE OF GLOMERULONEPHROSIS

DATE	BODY WEIGHT (KG.)	FOOD INTAKE							NITROGEN					
					NITROGEN (GM.)				EXCRETION				BALANCE	
		CALORIES PER 24 HR.	CHO (GM. PER 24 HR.)	FAT (GM. PER 24 HR.)	FOOD	CASEIN DIGEST		TOTAL PER KG.	URINE			FECES (GM.)	GM. PER 24 HR.	GM. PER KG. PER 24 HR.
						ENTERALLY	I.V.		TOTAL (GM.)	N.P.N. (GM.)	PROTEIN (GM.)			
9/ 9/40	14.7	1,719	137	85	9.13	4.80			9.74	8.23	1.51			
9/10/40	15.2	1,719	137	85	9.88	4.80			10.66	8.48	2.18			
9/11/40	15.6	1,719	137	85	10.77	4.80			11.40	9.62	1.78			
Average	15.2	1,719	137	85	9.93	4.80		0.97	10.60	8.78	1.82	1.69	+2.44	+0.16

the same with an increase in the stool nitrogen. The data on the third period in which casein digest was given by both oral and intravenous routes is not included because on more than one occasion vomiting occurred. During the last three balance studies the caloric intake was approximately 99 calories per kilogram, with an average of 0.78 Gm. nitrogen per kilogram, which was derived very largely from casein digest given orally. In these three periods the nitrogen balances were markedly positive, ranging from 0.11 to 0.19 Gm. per kilogram per day. It is of interest to note that between October 5 and October 24, while casein digest was the only appreciable source of nitrogen in the diet, the patient's serum total protein rose from 3.08 Gm. per 100 c.c. to 4.77 Gm., and the albumin from 1.03 to 2.10 Gm.

Interpretation.—When casein digest replaced the usual food protein, the patient remained in positive nitrogen balance with an increase in stool nitrogen. When the quantity of casein digest taken was increased by 100 per cent, the nitrogen retention increased appreciably.

CASE 8.—R. B., a 2½-year-old white boy, was in the hospital for over a year with the nephrotic type of glomerular nephritis. During this period he suffered from repeated episodes of infection and on several occasions was treated with one of the sulfonamides. During the entire period in the hospital, there was marked proteinuria which, at times, amounted to as much as 14 Gm. per day. Microscopic examination of the urine usually revealed occasional red blood cells and varying numbers of casts, quite frequently fatty in nature. The serum albumin was greatly reduced during the entire period of observation. On discharge from the hospital the total serum protein was 3.80 Gm. per 100 c.c., the albumin, 0.92, and the nonprotein nitrogen, 33 mg. per cent.

Casein digest (10 to 40 Gm. per day) was added to the patient's diet during nearly all of the seven-week period preceding the nitrogen balance study. The protein intake varied considerably; occasionally, it was very low but more often was between 0.3 and 0.6 Gm. of nitrogen per kilogram per day. Because of more or less persistent nausea with occasional vomiting, only one balance period was obtained. During this period the nitrogen intake averaged 0.97 Gm. per kilogram per day, approximately one-third of it being derived from casein digest. The patient was in marked positive nitrogen balance, retaining 0.16 Gm. per kilogram per day (Table VIII). This retention occurred while his urinary protein nitrogen averaged 0.12 Gm. per kilogram per day.

The patient returned home still with active nephritis and has continued to receive 40 Gm. of casein digest per day added to his regular diet. At the time of this writing, June 1, 1941, he continues to have intense proteinuria and usually has considerable edema.

SUMMARY AND CONCLUSIONS

In eight children the utilization of an enzymatic casein digest, Amigen, was studied when given in one or more of the following ways: (1) as a supplement to an ordinary diet; (2) as a replacement of meat, milk, and eggs in the diet; and (3) as the only appreciable source of nitrogen, given either enterally, intravenously, or by the combined enteral and intravenous routes.

Conclusions were as follows:

1. It was easily possible to increase an ordinary nitrogen intake of 0.4 to 0.6 Gm. per kilogram of body weight by 50 per cent or more when casein digest was given as a supplement to the regular diet.

2. When casein digest was given enterally as a substitute for meat, milk, and eggs, positive nitrogen balances were maintained at essentially unchanged levels.

3. When almost the entire food nitrogen was replaced by an equal amount of casein digest nitrogen administered enterally, nitrogen retention as observed in single three-day balance periods was essentially unaffected. When the casein digest intake was approximately doubled, nitrogen retention doubled or tripled. In one patient when casein digest was the only appreciable source of nitrogen and half was given enterally and half intravenously, the nitrogen retention equaled that observed when the entire amount of casein digest was given enterally as well as that when the nitrogen intake was derived from meat, milk, and eggs. In another patient in a similar study less nitrogen was retained when half of the casein digest was given enterally and half intravenously than when it was all given enterally or when meat, milk, and eggs were the chief sources of nitrogen. Because of the occurrence of reactions,* such as vomiting, chills, and fever, or phlebitis with edema, or because of unrelated intercurrent infections, attempts to obtain nitrogen balance data were unsuccessful when casein digest as the only appreciable source of nitrogen was given entirely by the intravenous route.

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*During the past year a much improved solution of Amigen has been furnished us by Mead Johnson & Co., and its use in concentrations of from 3 to 10 per cent is rarely followed by even mild reactions. In a later communication we intend to discuss the many clinical uses for intravenously administered solutions of Amigen.

ADDITIONAL PAPERS WHICH HAVE APPEARED SINCE THE COMPLETION OF OUR STUDY

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SHIGELLA PARADYSENTERIAE INFECTION IN MICE

Treatment With Sulfaguanidine and Sulfacetimide (Sulamyd)

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IN PREVIOUS publications[1, 2] we have presented data concerning the therapeutic value of various sulfonamide drugs in the treatment of mice experimentally infected with *S. paradysenteriae*. The sulfonamide drugs tested were sulfathiazole, sulfapyridine, sulfanilamide, and sulfamethylthiazole. The first two were more effective and sulfanilamide was the least effective.

The purpose of this report is to present additional information regarding the therapeutic value of two sulfonamide compounds which have become available more recently; namely, sulfaguanidine* and sulfacetimide† (sulamyd). The technique used was the same as that reported in the previous publications. Groups of ten mice were injected intraperitoneally with 1, 10, 100, and 1,000 minimum fatal doses of culture suspended in 3 per cent mucin. One minimum fatal dose contained approximately 8,000 bacteria. Three hours after injection of the culture each mouse was given one dose of the sulfonamide compound by stomach tube. All control mice died when injected with one minimum fatal dose of culture and not treated with the drug. Of the control mice injected with one-tenth of a minimum fatal dose of culture and not treated with the drug, 60 per cent died.

Data in Tables I and II indicate that when Flexner and Sonne types of *S. paradysenteriae* were used, one dose of 10 mg. of either sulfaguanidine or sulfacetimide was necessary to give therapeutic results comparable to those obtained with 1 mg. of either sulfathiazole or sulfapyridine. These doses were the minimum effective doses.

The blood levels obtained one hour after administration of these minimum effective doses of the sulfonamide compounds were quite different. In Table III it may be seen that 10 mg. of sulfaguanidine and 10 mg. of sulfacetimide, respectively, gave blood levels of 1.8 mg. per cent and 22.3 mg. per cent. Three hours after the single dose of these drugs all blood levels were less than 1 mg. per cent. It is interesting that here are two sulfonamide compounds equally efficient in the treatment of mice, experimentally infected with *S. paradysenteriae*, at a time in the course of their infection when they have an overwhelming septicemia,[2] the one drug, sulfaguanidine, giving a low blood level of 1.8 mg. per cent and the other, sulfacetimide, giving a high

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*Supplied by Lederle Laboratories.

†Supplied by Schering Corporation.

blood level of 22.3 mg. per cent. In a previous study[2] 1 mg. of sulfathiazole, the minimum effective dose, was found to give a blood level of 2.4 mg. per cent.

TABLE I

SHIGELLA PARADYSENTERIAE OF FLEXNER: MORTALITY AMONG MICE GIVEN SULFONAMIDES BY STOMACH TUBE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MINIMUM FATAL DOSES	SULFATHIAZOLE (1 MG.)	SULFAPYRIDINE (1 MG.)	SULFANILAMIDE (1 MG.)	SULFAGUANIDINE (5 MG.)	SULFAGUANIDINE (10 MG.)	SULFACETIMIDE (10 MG.)
1	0*	0	2	2	1	0
10	2	0	6	5	1	2
100	4	6	9	6	7	3
1,000	10	10	10	10		10

Each of forty control mice was given 1 minimum fatal dose and all died.
*Ten mice in each group.

TABLE II

SHIGELLA PARADYSENTERIAE OF SONNE: MORTALITY AMONG MICE GIVEN SULFONAMIDES BY STOMACH TUBE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MINIMUM FATAL DOSES	SULFATHIAZOLE (1 MG.)	SULFAPYRIDINE (1 MG.)	SULFANILAMIDE (2 MG.)	SULFAGUANIDINE (10 MG.)	SULFACETIMIDE (10 MG.)
1	1*	1	2	2	2
10	5	4	7	3	3
100	6	6	10	9	9
1,000	6	7	10	10	-
10,000	10	10	10	-	-

Each of forty control mice was given 1 minimum fatal dosage; all died.
*Ten mice in each group.

TABLE III

BLOOD DRUG LEVELS IN MICE*

DOSE (MG.)	SULFAGUANIDINE		SULFACETIMIDE	
	1 HR. (MG. %)	3 HR. (MG. %)	1 HR. (MG. %)	3 HR. (MG. %)
2	--	----	3.8	Less than 1
5	1.0	Less than 1	11.2	Less than 1
8	1.4	Less than 1	---	----
10	1.8	Less than 1	22.3	Less than 1
12	1.1	Less than 1	---	----
20	1.8	Less than 1	---	----
40	3.0	Less than 1	---	----

*Pooled blood from two mice used for each determination.

Additional information concerning blood levels following the administration of various amounts of the two newer sulfonamides may be found in Table III. Note that large doses of sulfaguanidine gave only low blood levels, as would be expected, while sulfacetimide gave high levels.

Such marked differences in blood levels associated with effective doses of two sulfonamides seem to indicate that a sulfonamide poorly absorbed

and giving low blood levels may be quite as effective as another sulfonamide readily absorbed and giving high blood levels.

CONCLUSIONS

In the treatment of mice experimentally infected with *S. paradysenteriae,* a single minimum effective dose of 10 mg. of either sulfaguanidine or sulfacetimide (sulamyd) gave therapeutic results comparable to those obtained with a single minimum effective dose of 1 mg. of sulfathiazole or sulfapyridine.

These effective doses of sulfaguanidine and sulfacetimide (sulamyd) gave blood levels of 1.8 mg. per cent and 22.3 mg. per cent, respectively.

Wide variations in blood levels were found following administration of effective doses of sulfonamide compounds. This is especially interesting in view of the fact that the infected mice had overwhelming septicemias at the time the drugs were administered by mouth.

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THE USE OF SULFAGUANIDINE IN ENTERIC INFECTIONS

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IN THE summer of 1940 Marshall and his associates[1] published an experimental study on sulfaguanidine. This drug has the unusual property of being fairly soluble in water but poorly absorbed from the intestinal tract. Due to this it is possible to produce a high concentration (200 mg. per cent) in the intestinal tract but a relatively low concentration (1 to 4 mg. per cent) in the blood. This drug should therefore, theoretically, be useful in combating enteric infections. Later, Marshall and his co-workers[2] reported the use of this compound in the treatment of acute bacillary dysentery. In their series there were seventeen patients with no controls.

Following this, Lyon[3] reported the use of this drug in the treatment of twenty-three patients with acute bacillary dysentery with an equal number of controls. Alternate patients were treated. Not all the patients were hospitalized, and stool cultures were done on approximately one-half of the patients.

FOREWORD

Bacillary dysentery is endemic in the eastern part of Kentucky. The number of cases varies widely from year to year but had shown a slight decline until the spring and summer of 1941, when the disease assumed epidemic proportions. This in part was due, no doubt, to a very dry season with a very occasional hard rain. Most of the patients came from the rural sections and mining camps where sanitation is not well advanced. According to the records of the Johnson County Board of Health, 50 per cent of the water supply of the rural areas shows pollution.

Acute gastroenteritis and bacillary dysentery still continue to lead all other diseases as a cause of mortality[4] in preschool children in Kentucky.

There has been a marked decline in the incidence of typhoid fever in eastern Kentucky due to the efficient work of the county health departments. Of the five patients with typhoid in this study, all came from the same locality and four from the same family. All had refused immunization and all had used the same water supply which was later proved to be polluted. The diagnosis was usually confirmed by stool culture and the Widal reaction. None of the patients had had any previous immunization.

PROCEDURE

In the spring of 1941, through the cooperation of Dr. E. W. Kissel of the Johnson County Board of Health and Dr. F. W. Caudill of the

Division of Communicable Diseases of the Kentucky State Board of Health, sulfaguanidine* was used in the experimental treatment of the enteric infections.

During the spring and summer of 1941, thirty patients with acute bacillary dysentery were selected for treatment at the Paintsville Hospital. Only those patients were selected who were moderately to severely ill. The basis for this classification was the general appearance of the patient, the degree of temperature, and the character and frequency of the stools. Of these three, the degree of temperature is the least reliable as a guide. As pointed out by Lyon,[5] dysentery is a disease with many vagaries. Often a child develops a temperature of 103 to 105° only to have the temperature return to an essentially normal level after two or three days although he may continue to have frequent stools containing blood and pus for one or two weeks.

Only those patients having diarrhea with a positive stool culture for the dysentery bacilli have been included in this series. The type of organism has, with one exception, been Hiss-Y dysentery. The Flexner organism, which has been encountered so frequently elsewhere,[6] was not found in this series.

Of these 30 patients with dysentery, 15 have received sulfaguanidine and the other 15 were used as controls.

In addition to the above dysentery cases, 5 patients with typhoid fever and 1 with Salmonella gastroenteritis have received sulfaguanidine. This organism was identified as *Salmonella paratyphi B* var. *java* by Edwards[7] of the National Salmonella Center of Lexington, Ky.

A detailed record has been kept on all patients. Of the 30 dysentery cases, all but 5 occurred in infancy and early childhood.

DOSAGE

The dosage followed has been that used by Lyon;[8] namely, 0.1 Gm. per kilogram of body weight for the initial dose, followed by 0.05 Gm. per kilogram every four hours. When the stools became less than five in twenty-four hours, 0.05 Gm. per kilogram was given every eight hours for forty-eight to seventy-two hours. This dosage has been followed with few exceptions.

In the typhoid cases, an initial dose of 0.1 Gm. per kilogram was given, followed by 0.05 Gm. per kilogram every four hours for one week.

The drug was practically tasteless and not unpleasant to take. It was usually given in a suspension of water.

On this dosage schedule there was one relapse to which more reference will be made in the appendix of case reports (Case 8-A). In one instance the drug was discontinued after sixty hours (Case 1-A) without a relapse.

*The author wishes to express his appreciation to the Lederle Laboratories for supplying the sulfaguanidine used in this study.

Sulfaguanidine was usually started immediately in those cases in which there was blood and pus in the stools and in which the diagnosis was reasonably certain. However, in those cases in which there was no blood or pus and the diagnosis was not well established, a positive stool culture was required before starting the drug. This was necessary in only two instances.

BLOOD CONCENTRATION OF SULFAGUANIDINE

Every patient treated with sulfaguanidine had at least one determination of the blood concentration. The method used was that originally recommended by Bratton and Marshall,[8] using 2 c.c. of blood. The concentration ranged from 1 mg. per cent to 3.6 mg. per cent. The average was 2.3 mg. per cent of the free drug. This was on a dosage schedule of 0.05 Gm. every four hours.

THE STOOLS

In order to get a composite picture of the character of the stools, at least one specimen was examined daily, and more when possible. The stools were regarded as checked when they numbered four or less in twenty-four hours, were formed, and contained no gross blood or pus. In the patients treated with sulfaguanidine, it was usually fairly easy to decide when the stools were checked, but in the control group the dividing line was never clear-cut and it was not always easy to decide. In several of the patients stool cultures were still positive after sulfaguanidine was discontinued.

As soon as possible after admission a stool specimen was sent to the laboratory and it was plated immediately on desoxycholate citrate agar and desoxycholate agar. These media were used because it was felt that they were superior to other media for the isolation of the dysentery bacilli. Usually three cultures were taken before the stool was called negative. Identification of the particular organism was completed by their carbohydrate fermentation reactions and agglutination with specific sera.

GENERAL TREATMENT

Both groups have received identical treatment except that no sulfaguanidine, sulfathiazole, or other sulfonamide compound has been given in the control group. No laxatives have been permitted. Pain, restlessness, and tenesmus were controlled by phenobarbital and camphorated opium. No bismuth preparations were used because they would have obscured the character of the stools.

In addition to the usual supportive measures, special attention was given to maintaining a good fluid intake, correction of acidosis, and insistence on a high vitamin intake. Many of the oral fluids were given as 5 and 10 per cent dextrose in physiologic saline. Acidosis was corrected by the use of either sodium bicarbonate or sodium lactate.

The diet was essentially a high protein, low carbohydrate, as protein milk, skimmed boiled cow's milk, or lactic acid milk. Temperatures were taken rectally except in adults. The temperature was recorded as normal when it remained constantly below 100.4° rectally and 99.4° orally. The admission temperature was the highest temperature recorded in the twenty-four hours following admission.

A blood count and urinalysis have been done at frequent intervals, usually daily. It has not been possible to do follow-up studies to detect any toxic effects of the drug.

In the typhoid cases particular attention was given to maintaining a high caloric intake. Pain and restlessness have been controlled by the use of opiates. The Salmonella gastroenteritis was treated the same as the dysentery cases.

CLINICAL OBSERVATIONS

Of the fifteen patients with dysentery treated with sulfaguanidine the results in thirteen were excellent, only fair in one (Case 7-A), and a complete failure in another (Case 3-A). In most cases the response was just as dramatic and spectacular as that obtained by the use of sulfathiazole and sulfapyridine in pneumococcic pneumonia. The temperature usually dropped to normal in twenty-four hours, and the general appearance of the patient changed from that of an acutely ill child to one who could scarcely be called ill in a period of forty-eight hours. When treated early there was usually a definite decrease in the toxicity of the patient and a slowing down of the stools by as early as twelve hours, and practically always by twenty-four hours. The remarkable improvement in the general condition of the patient was the most dramatic thing observed in this study. Often a child who was acutely ill on admission would be sitting up in bed and playing in thirty-six hours. In all but three patients the temperature returned to normal in twenty-four hours.

In one patient sulfaguanidine had no effect on the course of the disease and the child died on the ninth day (Case 3-A). He was a very poorly nourished male infant, 17 months old, weighing only 6 kilograms. The patient in Case 7-A was not admitted until the eighth day of the disease, and while he received some benefit from sulfaguanidine, improvement was slow.

A general idea of the differences between the two groups can be seen by comparing Charts 1 and 2. In general, the patients in the control group followed the course of the disease which has been observed in the past; however, there have been some rather wide variations. One patient died from an overwhelming toxemia only sixty hours after onset of illness (Case 14-B), while another patient made a very rapid recovery after an onset which would ordinarily indicate a virulent infection (Case 11-B).

No.	Age	Wt.*	Temp.	Stools First 24 Hrs.
1-A	2 yrs.	14	104	22
2-A	34 mos.	12	101	19
3-A	17 mos.	6	101	11
4-A	27 yrs.	70	103	10
5-A	20 mos.	10	103	10
6-A	7 wks.	4	103.2	18
7-A	5 mos.	7	103.4	22
8-A	5 mos.	7	102.6	16
9-A	7 mos.	9	103.4	17
10-A	66 yrs.	70	102.2	8
11-A	3 yrs.	15	104	22
12-A	4 yrs.	12	103.6	10
13-A	11 mos.	10	104	20
14-A	16 mos.	10	104	10
15-A	2 yrs.	12	105	25

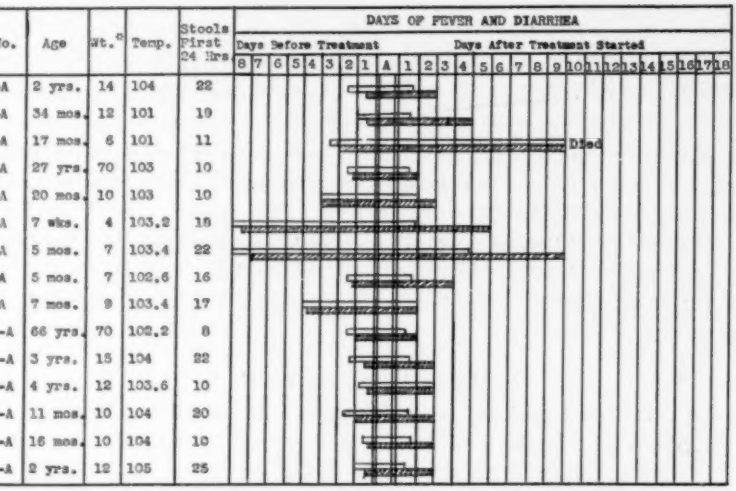
DAYS OF FEVER AND DIARRHEA
Days Before Treatment
Days After Treatment Started
8 7 6 5 4 3 2 1 A 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Died
Fever
Diarrhea
* - Weight in kilograms
A - Admission

Chart 1.—Dysentery patients given sulfaguanidine.

No.	Age	Wt.*	Temp.	Stools First 24 Hours
1-B	14 mos.	10	106	16
2-B	2 yrs.	12	104	11
3-B	14 mos.	10	103.3	8
4-B	4 mos.	6	103.2	20
5-B	9 mos.	8	102	18
6-B	1 yr.	6	101.4	35
7-B	16 mos.	10	103.4	7
8-B	33 yrs.	65	100	10
9-B	40 mos.	15	101	9
10-B	8 yrs.	24	101	15
11-B	30 mos.	14	105	8
12-B	28 yrs.	50	101.2	12
13-B	24 yrs.	48	101	16
14-B	8 mos.	8	105	
15-B	34 mos.	16	102	12

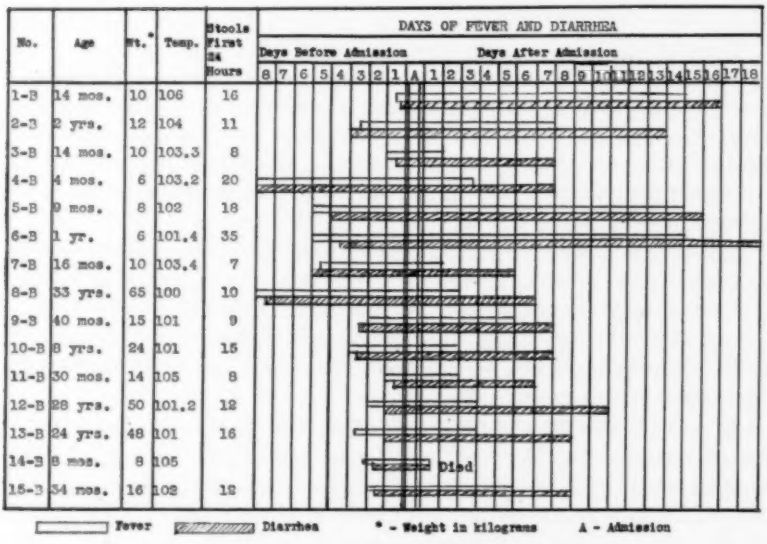
DAYS OF FEVER AND DIARRHEA
Days Before Admission
Days After Admission
8 7 6 5 4 3 2 1 A 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Died
Fever
Diarrhea
* - Weight in kilograms
A - Admission

Chart 2.—Dysentery patients not given sulfaguanidine.

Of the five patients with typhoid treated with sulfaguanidine, all ran a course essentially unchanged by administration of the drug. In no instance was there any marked change in the temperature or improvement in the general condition of the patient. Two of these patients had a very stormy course. One patient who was pregnant aborted in the fourth week of the disease. This was followed by two postpartum hemorrhages which required two transfusions to correct; she was not discharged until the seventh week. The other patient had repeated small hemorrhages.

The patient with the Salmonella gastroenteritis ran a course which was unaltered by administration of sulfaguanidine.

While the number of typhoid cases is too small to draw any definite conclusions as to the effectiveness of the drug in these conditions, it would indicate that very little is to be expected from the use of sulfaguanidine in the typhoid-paratyphoid infections. Its final status in enteric infections can be determined only by clinical use and study.

TOXIC EFFECTS

Very few toxic effects have been observed in this series of twenty-one patients. In one patient (Case 1-A) a tide of sulfaguanidine crystals appeared in the urine after forty-eight hours of therapy. No hematuria was associated with the crystals. After sixty hours the drug was discontinued and fluids forced. No other untoward effects were observed in this case.

Nausea was observed in two instances. This cleared, however, as soon as the drug was discontinued. One other patient complained of a very severe headache which cleared as soon as the drug was discontinued. While sulfaguanidine was certainly not known to have been the cause, it was thought to have been. A unilateral conjunctivitis developed on the third day of therapy in one of the typhoid patients. None of the patients developed rashes or drug fever. The leucocyte count varied from 3,700 to 15,250. No tendency to leucopenia or agranulocytosis was noted.

No other toxic manifestations associated with the sulfonamide drugs, such as hematuria, hemolytic anemia, or anuria, were observed. However, it should be emphasized that sulfaguanidine was not given longer than twelve days in any case.

In general, toxic manifestations were encountered much less frequently than those observed in the use of sulfanilamide, sulfapyridine, and sulfathiazole.

CONCLUSIONS

Sulfaguanidine is an effective chemotherapeutic agent in the treatment of acute bacillary dysentery.

It is most effective when administered in the first few days of the disease.

While the number of typhoid patients treated has been too small to draw definite conclusions, indications are that very little is to be expected from the use of sulfaguanidine in typhoid fever.

In general, toxic manifestations were encountered much less frequently than those observed in the use of sulfanilamide, sulfapyridine, and sulfathiazole.

SUMMARY OF CASES TREATED WITH SULFAGUANIDINE

CASE 1-A.—P. B., a white female, aged 2 years, and weighing 14 kilograms, was admitted on the first day of illness. Chief complaints were high fever, a convulsion, and diarrhea. In the twelve hours before admission she had passed 12 stools, containing blood, pus, and mucus. She was acutely ill but not dehydrated. Temperature was 104° and white blood count, 9,350. A stool culture was taken and the patient was started on sulfaguanidine. Stool culture later revealed Hiss-Y type of dysentery. Her temperature dropped to normal in twelve hours and there was a marked improvement in the general condition in twenty-four hours. In forty-eight hours the child appeared practically well. The stools dropped from 20 in the first twenty-four hours to 1 in the next twenty-four hours. After receiving sulfaguanidine for forty-eight hours, a tide of sulfaguanidine crystals appeared in the urine. The drug was discontinued twelve hours later and fluids forced. No other toxic symptoms were noted, and the child was discharged on the seventh day.

CASE 2-A.—S. C., white female, aged 34 months, and weighing 12 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. She was moderately ill and the history revealed that she had passed about 20 stools in the first twenty-four hours of illness, containing blood, pus, and mucus. Her temperature was 101° and white blood count was 15,050. Her stools contained more than the usual amount of blood, and the Hiss-Y type of organism was isolated from the stools. Sulfaguanidine was started immediately. Within eight hours her temperature was normal, and there was a very marked improvement in the general condition at the end of forty-eight hours. The improvement in the stools, however, did not parallel the improvement in her general condition, as they were not checked until the fifth hospital day. Sulfaguanidine was discontinued on the seventh day and the patient was allowed to go home on the same day.

CASE 3-A.—E. C., white, male, aged 16 months, weighed 6 kilograms at the time of his first admission. Chief complaints were fever and diarrhea. Five days before admission he had eaten some sandwich spread, containing pickles, olives, etc. Following this he began to have a diarrhea and fever. For the two days before admission he vomited everything taken by mouth and was reported to have had 30 loose, watery stools in the twenty-four hours before admission. At the time of admission he was very markedly dehydrated and critically ill. Carbon dioxide combining power was 28 vol. per cent. A continuous intravenous drip was started and sodium bicarbonate given to correct the acidosis. Within twenty-four hours he was much improved. Due to his very poor general condition, it was three weeks before he recovered. He was retained in the hospital two weeks longer to build up his general condition. Three stool cultures were negative and at no time during hospitalization was any gross blood or pus observed in the stools.

Second Admission.—He was readmitted eight days later with a history of a bloody diarrhea for two days. At this time he was acutely ill. Temperature was 101°. Sulfaguanidine was started immediately. The first stool culture was positive for

Hiss-Y dysentery. Despite sulfaguanidine, parenteral fluids, and repeated blood transfusions, his course was progressively downward and he expired on the ninth hospital day.

CASE 4-A.—V. C., white, female, aged 27 years, and weighing 70 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. In the fifteen hours before admission she had passed 14 stools and the last few contained blood, pus, and mucus. Her temperature was 103° and she appeared acutely ill. The leucocytes numbered 8,200. She was started on sulfaguanidine immediately. Stool culture was positive for Hiss-Y dysentery. Her temperature returned to normal in eighteen hours and the stools dropped from 10 in the first twenty-four hours to none in the next twenty-four hours. There was marked improvement in her general condition in the first thirty-six hours. On the third and fourth hospital days she complained of a severe headache. This was thought to be due to sulfaguanidine. The drug was discontinued on the fifth day. No other toxic symptoms were noted. Patient was discharged on the sixth day.

CASE 5-A.—C. W., white, male, aged 20 months, and weighing 10 kilograms, was admitted on the fourth day of illness. Chief complaints were fever and diarrhea. In the twenty-four hours before admission he had passed 12 watery stools. No blood or pus was seen in stools. He was moderately ill. Temperature was 103°. White blood cell count was 9,100. Hiss-Y type of dysentery was isolated from the stools within forty-eight hours, and he was then started on sulfaguanidine. His temperature was normal in eighteen hours and he was practically well on the third day. The stools dropped from 15 on the first day that sulfaguanidine was started to 3 on the second day and never numbered over 4 thereafter. Sulfaguanidine was discontinued on the sixth day and he was allowed to go home on the eighth day.

CASE 6-A.—C. B., white, male, aged 7 weeks, and weighing 4 kilograms, was admitted on the eighth day of illness. Chief complaints were fever and diarrhea. He was reported to have had a watery diarrhea for eight days preceding admission. He was moderately ill. Temperature was 103.2°, and a leucocyte count was 10,700. Hiss-Y dysentery was isolated from the stools on the second day and he was then started on sulfaguanidine. His temperature returned to normal in twenty hours, but the diarrhea was not checked until the fifth hospital day. Sulfaguanidine was discontinued on the eighth day and he was sent home on the eighth day.

CASE 7-A.—L. P., white, male, aged 5 months, and weighing 7 kilograms, was admitted on the eighth day of illness. Chief complaints were fever and diarrhea. On admission he was very acutely ill and dehydration was marked. His temperature was 103.4°, and the white blood cell count was 10,650. He was reported to have passed 20 to 30 stools daily. There was a small amount of blood and pus present in stools. The first stool culture revealed the Hiss-Y type of dysentery. He was started on sulfaguanidine on the first day. His temperature did not return to normal until the fourth day, and there was only a very gradual slowing down of the stools, nine days being required before they had returned to normal. The improvement in his general condition, however, was slightly better than that observed on the stools and temperature. Sulfaguanidine was discontinued on the ninth day and he was allowed to go home on the tenth day. While the response to sulfaguanidine was certainly not as marked as in some other cases, it undoubtedly was beneficial.

CASE 8-A.—L. C., white, male, aged 5 months, and weighing 7 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. He was admitted to the hospital moderately ill. Temperature was 102.6°, and a leuco-

cyte count was 10,000. In the twelve hours before admission he had passed 8 watery stools, containing blood, pus, and mucus, from which the Sonne type of dysentery was isolated. Sulfaguanidine was started immediately. Within a period of fourteen hours temperature returned to normal, and the general condition was much improved in twenty-four hours. Blood and pus did not disappear from the stools until the fourth day. The stools numbered 16 in the first twenty-four hours and never over 3 in any following twenty-four-hour period. He was practically well on the fourth day. Sulfaguanidine was discontinued on the seventh day, and he was allowed to go home.

Second Admission.—On the third day after going home his stools again became loose, and blood, pus, and mucus were present. He was readmitted two days later. At the time of second admission he did not appear very ill. Temperature was 99.8°, and leucocyte count was 8,100. Stool culture was again positive for Sonne dysentery. He was started on sulfaguanidine. The stools dropped from 7 in the first twenty-four hours to 2 in the next twenty-four hours and thereafter never numbered more than 1 daily. Blood was present until the sixth day. Sulfaguanidine was discontinued on the eighth day, and he was allowed to go home on the ninth day.

CASE 9-A.—S. S., white, male, aged 7 months, and weighing 9 kilograms, was admitted on the fourth day of illness. Chief complaints were high fever, and diarrhea. In the twenty-four hours before admission he had passed about 30 loose, watery stools, containing very little blood, pus, and mucus. He was acutely ill and slightly dehydrated. Temperature was 103.4°, and a leucocyte count numbered 7,850. Stool culture was positive for Hiss-Y type of dysentery. Sulfaguanidine was started immediately. Within a period of twelve hours he appeared brighter, and the stools were beginning to slow down. His temperature dropped to normal in twenty hours and he was practically well on the second day. The stools numbered 17 on the first day and dropped to 2 on the second day. He was taken home on the third day against advice; however, there was no relapse.

CASE 10-A.—S. J., male, aged 66 years, and weighing 70 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. In the twelve hours before admission he had passed 8 stools, containing blood, pus, and mucus. He appeared moderately ill. Temperature was 102°, and a white blood count was 9,700. Stool culture was positive for Hiss-Y type of dysentery. Sulfaguanidine was started immediately. Within eight hours his temperature was normal. His stools numbered 8 on the first day and never over 2 on any following day. Sulfaguanidine was discontinued on the fourth day and he was allowed to go home.

CASE 11-A.—J. L., white, male, aged 3 years, and weighing 15 kilograms, was admitted on the second day of illness. Chief complaints were high fever, convulsions, and diarrhea. In the twelve hours before admission he had had three convulsions and was admitted while having the fourth. His stools contained blood, pus, and mucus. Temperature was 104°. White blood cell count was 7,950. After a short period of sedation he was started on sulfaguanidine. Within a period of ten hours there was a definite decrease in the toxicity, and his temperature was normal in eighteen hours. Stool culture revealed the Hiss-Y type of dysentery. Within forty-eight hours he was practically well. The stools numbered 22 in the first twenty-four hours and 2 in the next twenty-four hours, and blood was absent forty-eight hours after sulfaguanidine was started. Sulfaguanidine was discontinued on the fourth day and he was allowed to go home on the same day.

CASE 12-A.—J. P., female, aged 4 years, and weighing 12 kilograms, was admitted on the first day of illness. Chief complaints were convulsions, fever, and diarrhea. She was admitted to the hospital while having a convulsion. She was

reported to have had three other convulsions in the twelve hours before admission. She was having frequent bloody stools from which Hiss-Y type of dysentery was isolated. Her temperature was 103.6° and a leucocyte count was 10,200. Sulfaguanidine was started. Within eight hours there was a marked drop in temperature (100.4°) which was followed by a slight secondary rise. After forty-four hours temperature returned to normal. Her stools numbered 10 the first day and none the second day. The improvement in her general condition was rapid and she was well by the third day. Sulfaguanidine was discontinued on the fifth day, and she was allowed to go home on the sixth day.

CASE 13-A.—F. P., white, male, aged 11 months, and weighing 10 kilograms, was admitted on third day of illness. Chief complaints were fever and diarrhea. He was reported to have had 20 stools, containing blood, pus, and mucus, in the twenty-four hours before admission. Temperature was 104° and white cell count was 7,150. Sulfaguanidine was started immediately. Stool culture revealed the Hiss-Y type of dysentery. Within twenty hours his temperature was normal and he appeared well on the third day. His stools numbered 20 on the first day and 3 on the second day. Sulfaguanidine was discontinued on the fifth day and he was allowed to go home.

CASE 14-A.—J. M., white, female, aged 16 months, and weighing 10 kilograms, was admitted on the first day of illness. Chief complaints were fever and bloody diarrhea. She was admitted to the hospital after an illness of only ten hours. At this time she was passing very loose stools with a moderate amount of blood, pus, and mucus. The first stool culture was positive for the Hiss-Y type of dysentery. At the time of admission she appeared acutely ill. Her temperature was 104° and white blood cell count was 10,450. Sulfaguanidine was started. Within twelve hours her temperature had returned to normal and she appeared much better. She was well by the third day. Her stools numbered 10 the first day and 1 the following day. Sulfaguanidine was stopped on the fourth day and she was sent home.

CASE 15-A.—F. A., white, male, aged 2 years, and weighing 12 kilograms, was admitted on the second day of illness. Chief complaints were fever, a convulsion, and diarrhea. He was admitted to the hospital while having a convulsion. He was reported to have had about 25 stools, containing blood, pus, and mucus, in the twenty-four hours before admission. Temperature was 105° and a leucocyte count was 7,700. Stool culture was positive for Hiss-Y type of dysentery. Sulfaguanidine was started after a short period of sedation. Within eight hours his temperature had returned to normal and he appeared well on the third day. He had 20 stools on the first day and they did not exceed 4 on any day thereafter. Sulfaguanidine was discontinued on the fourth day and he was allowed to go home on the fifth day.

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INTRAPULMONARY PRESSURES IN THE NEWBORN INFANT

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WITH THE TECHNICAL ASSISTANCE OF
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EXTRAUTERINE respiration begins as an antagonism between (a) those factors tending to resist pulmonary expansion and (b) those factors tending to produce pulmonary expansion, and, by so doing, to draw air into the pulmonary alveoli. In order to discuss this balance of forces intelligently, it is necessary to describe its components in terms of mathematical measurements. These cannot be simply supplied from the facts of adult physiology, as the strength with which the lungs normally resist expansion at birth is much greater than is the case thereafter. This has been determined by the experiments of Wilson and Farber[1] upon atelectasis, as well as by recent confirmatory observations of our own.[2] The force available to the infant for overcoming this resistance has not until now been reported in terms of mathematical units. An attempt to secure such measurements in a series of newborn infants forms the subject of the present communication.

Wilson and Farber showed not only that the cohesion of moist alveolar surfaces in the unexpanded lung offers a basic opposition to inflation, but also that certain other hindrances, such as the aspiration of foreign substances or the peculiar state of the premature lung, might often be added to this invariable circumstance. The sum of these conditions, which can be grouped together under the general heading of *resistance*, may be expressed in terms of the pressure with which it resists expansion. Wilson and Farber,[1] whose observations were concerned with the lungs of premature infants, found that this resistance was equal to a pressure of 25 to 30 cm. of water, and might, in some infants, be even greater than that. Our own experience with the lungs removed at autopsy from some forty newborn infants agrees with these figures. Rarely does noticeable expansion begin to appear when the lungs are subjected to air under pressures of less than 20 cm. of water and often nearly 30 cm. are required, even in the lungs of full-term infants such as most of those we examined. It should be pointed out that the resistance may be broken either by the application of sufficient *negative* pressure over the pleural surface of the lung or by the introduction of air under an identical degree of *positive* pressure into the trachea, but whichever method is used the forces of resistance will consistently equal that of a column of water 20 to 30 cm. high.

On the other side of the respiratory balance, and as yet unmeasured, is the inflating or expanding effort which the infant's thoracic mechanism

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can bring to bear upon the lungs. Obviously the fact that the great majority of infants survive the change from placental to pulmonary respiration testifies to the superiority of the expanding force as compared to the resisting one, but the margin of safety cannot be stated unless actual measurements are available for comparison with the 20 to 30 cm. of water known to be exerted by the forces of resistance. The question is not merely an academic one since intelligent efforts at mechanical resuscitation of the newly born cannot be made without some knowledge of the degree of natural force which is to be supplemented or imitated.

Schmidt[3] states that the greatest intrapulmonary negative pressure occurring with forced inspiration against obstruction in the adult may equal –70 mm. Hg, which is the equivalent of –94.5 cm. water. Under such circumstances the intrapleural pressure, as measured by a manometer connected with the pleural space, may become –70 to –80 mm. Hg, or –94.5 to –108 cm. water. The intrapulmonary pressure may be expected to differ from the intrapleural in proportion to the flexibility of the lung tissue. If the elastic fibers and other components of the lung parenchyma offered no resistance whatever to thoracic movement so that the lung followed the thoracic wall effortlessly, the intrapulmonary and intrapleural pressures would be identical at all times. The less flexible the lung tissue, the less negative will be the intrapulmonary pressure as compared to that in the pleural space. Thus an intrapleural pressure of –20 might produce a pressure of –18 in the alveoli of a very flexible lung, but a pressure of only –10 in the alveoli of a very sluggish, edematous one. Obviously, the intrapulmonary pressure can never be *more negative* than the intrapleural, and it is probably always appreciably *less negative*. The differences between the two pressures must certainly be most marked at the maximum degree of forced inspiration, the moment the lung is put most "upon the stretch" and the moment of the respiratory cycle with which this study was most concerned. The correctness of this reasoning has been substantiated by the observations of Barach[4] and could be demonstrated with a simple mechanical model in which a rubber balloon, its mouth connected with a manometer, was suspended in a glass jar. Momentary diminution of pressure in the jar was recorded by a second manometer. With a very thin-walled balloon, negative pressure readings were practically the same by both manometers; within a less flexible balloon there was much less negative pressure than that in the jar around it. The jar may be compared to the thorax, the balloon to the lung; the pressures in the jar are "intrapleural," those in the balloon "intrapulmonary." This same arrangement of two manometers and a vacuum jar were used occasionally with lungs removed from stillborn infants at autopsy. It was found that with a pressure in the jar of –25 cm. water, the manometer connected with the trachea registered just below –20 cm. The intrapulmonary pressure during inspira-

tion being thus a conservative measure of the intrapleural situation, we therefore adopted the intrapulmonary measurement for use in our observations and thus avoided the dangers which might have resulted from pleural puncture in a series of small infants.

METHODS

Data representing the intrapulmonary pressure conditions can be secured from any short system which, without important friction or dead space, forms a continuation of the trachea, nose, and mouth. As part of such a system a small mask was applied to the infant's face, the contact being made airtight by the use of boric acid ointment. From the mask a short length of wide rubber tubing led to a variable obstruction in the form of a tap which could be gradually or suddenly closed, and between the face and the obstruction a side arm led off to a manometer which thus registered the pressure in the mask, the trachea, and the

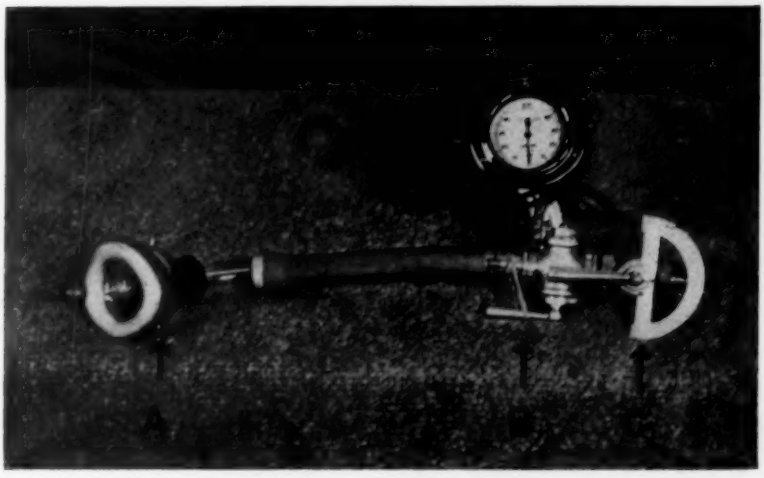

Fig. 1.—Apparatus for measuring intrapulmonary pressures. *A*, Small mask to cover infant's face, connected by glass and rubber tubing to *C*, an adjustable obstruction (tap) which is completely open at 0 degree position of handle and completely closed at 90 degrees. Between the mask and the obstruction a side-arm leads off at *B* to the aneroid manometer which registers the pressure in the tubing, and thus in the mask, trachea, and lungs. (The handle opposite the manometer at *B* was not used in this work.)

lungs (Fig. 1). During ordinary respiration through the opened tap, no pressure variations from zero were shown by the manometer, since the system offered no obstruction to the free passage of air. As the tap was slowly turned toward closure, a degree of obstruction was reached at which some infants would maintain respiration for perhaps thirty seconds or more without crying but with the use of obvious effort, the degree of which was indicated by the manometer. This very roughly indicated something of the infant's powers for continued and submaximal

respiratory activity under stress. Beyond this point, either because the infant became increasingly apprehensive or because the tap was fully closed as part of the experiment, or, usually, for both of these reasons, so much struggling and crying occurred that the infant appeared to be calling upon his maximal respiratory forces.

During the periods of submaximal dyspnea which we called "maintained" respiratory effort, the positive and negative pressures of expiration and inspiration were both recorded. Usually the negative pressure was of a slightly greater degree than the positive, although there were exceptions. It seemed misleading to record the positive pressure of expiration when the infant was crying in maximal respiratory activity, as his partially closed glottis was then introduced during expirations between the lungs and the manometer. Because of this interference with registration of true intrapulmonary circumstances, and because the maximal expiratory pressures were not of particular interest to us, only the negative pressures were recorded during this maximal period.

RESULTS

The intrapulmonary pressures of forty-seven infants obtained in this manner are presented in Table I. The youngest infant was examined ten minutes after birth; the smallest weighed 2 pounds, 12 ounces. The general level of the desired information became apparent very soon after we began to examine these patients, results considerably greater than had been anticipated repeating themselves almost monotonously. Unfortunately the aneroid manometer used was not calibrated above 40 cm. of water, and a large percentage of the babies produced pressures which carried the needle of the instrument above this mark. The figures in column C of the table are thus often not the actual maximal values. They do, however, form data more significant than those in the other columns since they must indicate, nearly, the greatest force the normal infant can throw into action against resisting lung tissue, whereas the figures in columns A and B are merely very general evidences of power to continue breathing against difficulties.

In a few particular aspects interesting manifestations repeatedly appeared, and while none of these lent itself to exact measurement, some of them deserve comment. One striking finding was the relationship between the somnolence or irritability of the infant and the degree of intrapulmonary force with which he responded to the experiment. Thus, those (such as Nos. 3, 7, 10, and 12) examined during the first hours of life whose maximal inspiratory pressures went only to –25 or –30 were very obviously infants who, even with a certain amount of superficial stimulation, refused to cry. Occasionally a sluggish baby, seemingly incapable of much effort, would become aroused to greater activity, always with an accompanying increase in the inspiratory force being recorded. On the other hand, some refused to exert themselves and prac-

TABLE I*

INTRAPULMONARY PRESSURE (IN CM. H_2O)

INFANT NO.	AGE	WEIGHT	MAINTAINED A (POS.)	MAINTAINED B (NEG.)	MAXIMUM C (NEG.)	REMARKS
1	10 min.	8 lb.	10	15	40+	
2	15 min.	7 lb., 14 oz.	12	10	38	
3	15 min.	7 lb., 8 oz.	12	10	32	Sleepy; cried little
4	25 min.	7 lb.			37	Cried constantly
5	30 min.	7 lb., 7 oz.	15	10	40+	Sleepy
6	50 min.	6 lb., 5 oz.	10	12	35	
7	1½ hr.	7 lb., 12 oz.	10	5	25	Would not cry
8	2 hr.	8 lb., 4 oz.			35	
9	3 hr.	6 lb., 9 oz.	8	15	40	
10	3 hr.	8 lb., 15 oz.	8	12	30	Would not cry
11	3½ hr.	7 lb., 9 oz.	8	15	30	
12	5 hr.	8 lb., 10 oz.	10	15	25	Would not cry
13	5 hr.	8 lb., 8 oz.			40	
14	6 hr.	7 lb., 12 oz.			40+	Cried constantly
15	7 hr.	9 lb.			40+	Cried constantly
16	7 hr.	7 lb., 6 oz.	10	15	38	
17	7 hr.	6 lb., 11 oz.			40+	Cried constantly
18a	7 hr.	7 lb., 7 oz.	15	15	25	Sleepy; would not cry
19	8 hr.	7 lb., 9 oz.			40+	Cried at once
20	12 hr.	7 lb., 14 oz.	20	20	40+	
21	12 hr.	6 lb., 4 oz.	8	15	40	
22	12 hr.	6 lb., 6 oz.	20	20	35	
23	14 hr.	7 lb.	20	20	40+	"Acidotic," hyperpneic
24	30 hr.	6 lb., 9 oz.	20	25	40+	
18b	31 hr.	7 lb.	10	15	40+	
25	2 days	7 lb.	20	35	40+	
26	2 days	8 lb., 2 oz.	15	25	40+	
27	11 days	8 lb., 5 oz.			40+	Immediate crying
		IMMATURE INFANTS				
28	6 hr.	5 lb., 8 oz.	8	12	25	Sleepy
29	10 hr.	5 lb., 11 oz.			40+	Cried at once
30	2 days	5 lb., 8 oz.			40+	Cried at once
31a	7 days	5 lb., 8 oz.	20	25	30	Multiple deformities; weak infant; never cried well
31b	8 days	5 lb., 6 oz.	14	18	28	
31c	9 days	5 lb., 5 oz.	8	15	25	
32	9 days	5 lb., 3 oz.	10	15	32	
33	9 days	5 lb., 1 oz.	20	25	40+	
34	17 days	5 lb.			40–	Cried at once
		PREMATURE INFANTS				
35	1 day	4 lb., 8 oz.	10	15	40	Definite sternal retraction
36	3 days	4 lb., 14 oz.	10	12	40+	
37	6 days	4 lb.			40+	Cried at once
38	6 days	4 lb., 5 oz.			40+	Cried at once
39	7 days	4 lb., 4 oz.	20	20	40+	
40	10 days	4 lb., 12 oz.	10	20	40+	
41	13 days	4 lb., 9 oz.	10	15	40+	
42	5 days	3 lb., 12 oz.	10	12	40+	
43	12 days	3 lb., 13 oz.			40	Cried at once
44	27 days	3 lb., 4 oz.			32	Cried at once
45	44 days	3 lb., 10 oz.			32	Became cyanotic
46	14 hr.	2 lb., 12 oz.	5	8	26	
47	8 days	2 lb., 15 oz.			40+	Cried at once

*The intrapulmonary pressures of forty-seven newborn infants as maintained for several breaths against partial obstruction (A and B) and maximum negative pressure (C) during inspiration against partial or complete obstruction.

tically gave up the struggle after a few attempts; they remained apneic until the mask was removed and they were stimulated to breathe in its absence. These periods of apnea were not marked by cyanosis, nor did cyanosis develop in the interval of perhaps thirty seconds before the infant could be stimulated to draw an unobstructed breath.

This dependence of the respiratory force upon the liveliness of the subject does not completely explain the somewhat lower respiratory competence of the infants during the first few days of life, as another impression, reflected in columns A and B of the results, was that the infants actually did become possessed of more thoracic force with the passage of time. It will be noted that among the somewhat older infants (Nos. 16 to 27) positive and negative pressures of 20 and more cm. were often maintained. On the other hand, such pressures rarely appear in columns A and B for infants Nos. 1 to 11, who were examined during the first three hours of life. The infants may not have used their full efforts during the first few hours because of somnolence and a low degree of irritability, but there is also some reason to believe that their available forces were actually weaker than those appearing a short time later.

Another point of interest was the appearance of the external thorax and neck while the most powerful inspirations were taking place. It was anticipated from clinical experience that many infants, particularly the premature and immature ones, would show a collapsing inward of the thorax or a tugging inward of the trachea as the diaphragm exerted its downward pull and the intrapulmonary negative pressure reached its maximum against the obstruction. In the entire group this manifestation was noted only once, in infant No. 35, each of whose major inspiratory efforts resulted in a quick retraction of the sternum. Interestingly enough, this retraction was also present to the same general degree when the infant inspired without any obstruction or mask whatever. In all the other subjects, including the premature ones, the thoracic structures seemed sufficiently rigid to withstand the strains involved. Unfortunately it has not yet been possible (and it might be highly undesirable) to measure by this technique the inspiratory power of those infants so often encountered in nurseries for the premature, whose anterior chest walls collapse inward deeply with each ordinary inspiration.

Infant No. 31 was the subject of investigations on three succeeding days, during which time he showed a progressive decrease in maximum as well as submaximum intrapulmonary pressures. This was a baby with hydrocephalus, a large lumbar myelomeningocele, and multiple deformities of the extremities with flaccidity of the lower ones. The infant lost weight and strength, as was reflected by these tests as well as by the usual clinical signs, and died on the fifteenth day of life. Unfortunately permission for necropsy was not obtained so that we cannot know whether the −30 cm. intrapulmonary pressure exhibited in the first test was sufficient to overcome any primary atelectasis which may have been

present. The observations indicate the presence of a relationship between respiratory efficiency and general health even during earliest infancy.

The premature infants were not examined as early in their lives as were the others in the table. To apply data secured at 8 days or even at 1 day of age to the balance between resisting and expanding forces immediately after birth would be to risk a probable error of some magnitude. Nevertheless, the fact that infants of 4 pounds and less did produce maximum negative pressures of –40 cm. and more perhaps gives some information as to the forces which the premature infant's lungs may be capable of withstanding without important rupture or hemorrhage.

DISCUSSION

Under conditions of forced inspiration, newborn infants, whether mature or immature, appear to be capable of exerting intrapulmonary (and thus intrapleural) pressures which are about half as strong as those of adults. The margin of safety between the –40 cm. water negative pressure which is probably available to the average crying infant at birth and the 20 to 30 cm. which various features of his lungs impose in the way of resistance seems fortunately to be a sufficiently wide one, although this margin of safety must diminish considerably in the case of sickly or premature infants. Such a sharp increase in intrapulmonary pressures, and therefore in the forces making for expansion, is exhibited by the crying and struggling infant that the process of stimulating the newborn baby to cry gains considerable recommendation from these observations. The stimulation should not be thought of as merely an induction of breathing but as an induction of sufficiently forceful breathing to overcome at least some of the natural resistance. The whole matter of "stimulation" requires consideration also in terms of the harm which rough handling may produce in a delicate organism. Stimulation may do other things than stimulate.

The response of the newborn infant to artificially imposed respiratory difficulties, or to further respiratory difficulties than those he already faces, is interesting to observe. As indicated in the preceding section, the less irritable babies may sometimes simply abandon the struggle and lapse into apnea when complete obstruction of airway is imposed. Whether this apnea would have proved merely a temporary phenomenon (as Haldane[5] described when respiration is interrupted by obstruction), and whether an inspiratory or expiratory impulse would ultimately have broken through from the centers controlling respiration, the author did not wait to determine. An inference may be drawn, however, by comparing our observations with the tracings given by Haldane[5] which show that when respiration is interrupted (in the adult) by a sudden complete obstruction, the intrapulmonary pressure gradually and progressively rises or falls thereafter, the direction being determined by whether the obstruction was interposed at the end of inspiration or ex-

piration. Some activity of the respiratory muscles is thus going forward, even though it may not progress to the degree which breaks through the obstruction. With these particular infants, on the other hand, no such rise or fall in intrapulmonary pressure appeared on the manometer when respiratory efforts ceased in the face of a handicap. No effort to breathe, however weak, occurred. The impression, and it can be called no more than that, suggests that a somewhat less rugged mechanism is operating in the newborn infant.

It has long been a concern of those sponsoring or using mechanical devices for resuscitating infants at birth that no forces be used which might cause alveolar rupture or vascular damage in the lung. Murphy and Bauer[6] have been particularly cautious in warning that in respirators of the negative pressure type the maximum force should be no greater than –15 cm. water. Although this might advantageously supplement the efforts of the infant himself, it could not be expected to expand the lungs of many apneic infants, as it is less than the forces of resistance described above. Kreiselman[7] advises an upper limit of 21.6 cm. for positive pressure applied over the face, Henderson[8] speaks of $\frac{1}{100}$ of an atmosphere (7.6 mm. Hg, or 10.3 cm. water); and Flagg[9] allows 25.4 cm. water as a maximum. Wilson, Torrey, and Johnson[10] have come to the conclusion that pressures of 18 mm. Hg (24.4 cm. water) are not great enough to expand the lungs of stillborn infants but are too great to be withstood by the lung parenchyma. How the surviving infants overcome the problem imposed by these circumstances is not stated. Various resuscitating devices currently on the market stipulate that maximal pressures in some cases as low as 10 mm. Hg or 13.5 cm. water are not to be exceeded because of the danger of trauma to the lungs.

Such low forces would certainly be of doubtful efficacy for overcoming the resistance which the lungs are known to impose. Moreover the upper limit of safety would appear to be considerably higher than that recommended by manufacturers and sponsors in general. The argument is open to question. Nevertheless, since it has been determined that the infant at birth may subject the contents of his thorax to –40 cm. of tension with each powerful cry, it seems justifiable to approach that level in the use of mechanical devices. If a certain amount of disturbance to alveolar and vascular structures occurs in the process, one can only say that the same conditions would have been brought about had the infant himself been able to exert his normal efforts.

SUMMARY

A pressure of from 20 to 30 cm. water is usually required to overcome the factors resisting the expansion of the human lung at birth. To determine how much force the thorax of the newborn infant can exert against this resistance, the intrapulmonary pressures of forty-seven infants in the first few days of life were measured during respiration

against partial or complete obstruction. Most of the thirty-four infants weighing more than 5 pounds developed intrapulmonary pressures of –40 cm. water during maximal inspiratory effort; ten of thirteen premature infants also achieved pressures of this degree, the other three reaching –26 and –32 cm. water. Collapsing inward of the chest wall was observed in only one infant. More correlation was observed between intrapulmonary pressure and general irritability and activity, than between intrapulmonary pressure and size or maturity of the infant.

CONCLUSIONS

To overcome the initial resistance of the lungs at birth usually requires a force equal to that of 20 to 30 cm. water.

Measurements of the intrapulmonary pressure of newborn infants made to breathe against obstruction indicate that the infant is able to exert inspiratory forces which are well above this level. Many infants in the first hours of life can attain an intrapulmonary negative pressure greater than –40 cm. water, or about one-half the maximum attainable by adults.

Earlier work here reviewed has indicated the minimum pressure levels which may be necessary in the use of mechanical resuscitating devices for the newborn infants.

This study suggests the upper limits of pressure which might be considered safe or at least "physiologic" when brought about by such devices.

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SUDDEN DEATH IN INFANTS WITH SCURVY

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WE HAVE recently had an opportunity to review the clinical histories and pathologic findings in a group of children dying with varying degrees of scurvy. In three of these infants death came suddenly and quite unexpectedly. At autopsy all showed bone changes indicative of severe vitamin C deficiency; two had hypertrophy of the right ventricle of the heart. In each patient careful gross and microscopic examinations failed to reveal any other cause for death. It is to draw attention again to the role vitamin C deficiency may play in leading to cardiac insufficiency that the following cases are being recorded.

CASE REPORTS

CASE 1 (A-7051).—A colored female infant was first brought to the Harriet Lane Dispensary at the age of 11 days with the complaint of "peculiar breathing and breath-holding spells." Although her delivery, which took place at home, was rather difficult, she breathed well immediately. Twelve hours later, however, she stopped breathing, went limp, and her lips turned blue. After this episode she seemed well enough until a few hours before coming to the dispensary when she was seen to stop breathing again several times. The examiner noted that the infant held her breath and then coughed up some white mucus. The examination otherwise was negative. She was sent to the Baltimore City Hospitals where calcium gluconate was administered. She had three similar attacks during the first five hours there but no recurrence during the following seven days of her stay. At 2 months of age she was brought again to the dispensary because of watery stools and vomiting of two days' duration. Her formula was changed and she improved. Her next visit was at the age of 6 months when diarrhea and vomiting occurred again. At this time beading of the ribs was noted and a diagnosis of rickets was made. She was not seen again for four months and then was brought in dead by her mother who said she had gone to "dry her off" in the evening and found her lifeless. She had been perfectly well all that day. Post-mortem blood and spinal fluid cultures were sterile. There was no feeding history obtained other than the formula of 12 ounces of water, 6 ounces of Pet milk, and 1 tablespoon of sugar, advised at 3 months of age. There is no record as to whether orange juice or cod-liver oil had ever been given.

At autopsy (No. 16331) the following positive findings were noted. The body weighed 6 kg. The heart was obviously enlarged, weighing 65 Gm. This increase in size was due to hypertrophy of the right ventricle. All the valves were delicate and competent. The foramen ovale and ductus arteriosus were closed. The left ventricle did not seem enlarged. The myocardium of both ventricles was pale. The lungs contained fluid. The liver was yellowish. The line of ossification of the ribs was distinctly widened; the cartilage was movable on the shaft and the periosteum stripped from the cortex with a fair amount of ease. The meninges were delicate, and there was no evidence of hemorrhage.

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Microscopically the myocardium of both ventricles was normal. The liver showed atrophy of the central cells and a good deal of fatty infiltration. The pulmonary alveoli contained fluid. The ribs showed characteristic changes of marked scurvy with virtually no healing. There was no microscopic evidence of rickets.

CASE 2 (H. L. H., 96642).—An 11-month-old colored male infant was brought to the Harriet Lane Dispensary with the following story. About 6 weeks before he had developed a nasal discharge, cough, and fever. He vomited also and was quite sick for two weeks and then seemed to improve, although soon thereafter he developed swollen knee joints. There was no fever and he did not seem very sick but he did not get any better either. At 1 A.M. the morning of admission he began to cry. His legs seemed more tender and even the covers on them made him scream. He was brought to the hospital shortly after. It was then learned that he had always been a feeding problem, having refused almost all solid foods. Cereal in milk had been given for the past six months. He spat up practically all the orange juice, cod-liver oil, and vegetables which were offered. On examination the child's legs were distorted, being large with wide shafts. He looked wan and pale. He did not seem in extremis and the mother was told the condition could be treated. Almost immediately, however, the baby's body stiffened, his back arched, and his eyes rolled up. By the time the clothes were removed and 64 mg. of caffeine were administered, he was gasping at very infrequent intervals; the pulse was impossible to feel and the heart sounds were faint. Artificial respiration was administered but without avail.

At autopsy (No. 15167) the following positive findings were noted. The body weighed 6.5 kg. and its nutrition was fairly good. The heart was dilated but not enlarged for the age, weighing 50 Gm. There were punctate hemorrhages beneath the epicardium and in one pulmonic valve cusp. There were hemorrhages in the gums, tongue, and lungs. The costochondral junctions were broadened and there was hemorrhage beneath the periosteum. The cranial cavity was not examined but the cerebrospinal fluid removed was clear. Blood culture was sterile.

Microscopically the heart was normal. The bones showed characteristic changes of extreme scurvy without rickets.

CASE 3 (A-15620).—A 7½-month-old white male infant was brought to the Harriet Lane Dispensary gravely ill, and he died one-half an hour later. It was learned that six hours before the child had become blue and seemed to have difficulty in breathing. On examination the child appeared extremely cyanotic with slow and deep respirations. The costochondral junctions were sharply beaded. The child died suddenly just before a blood culture was to be taken. Post-mortem culture was sterile. The home was visited by a social service worker later who obtained the following information about the child's feeding. At birth he received a formula consisting of 2 ounces of milk powder, 2 ounces of water, and 1 teaspoon of sugar every four hours. He was said to have been given 1 to 2 ounces of orange juice three to four times a week, when the family could afford to buy oranges. At 4 months of age the diet was increased by the addition of chicken broth and canned vegetables. Cereal and cod-liver oil were never included. Recently the father had had work and 2 ounces of orange juice were given every day.

At autopsy (No. 16885) the following positive findings were noted. The body weighed 5 kg. The heart was enlarged, weighing 48 Gm. This was due to hypertrophy of the right ventricle. The myocardium was pale. The valves were delicate and competent; the foramen ovale and ductus arteriosus were closed. The lungs contained fluid. The line of ossification of the ribs was irregular; the cartilage was

freely movable on the shaft, and the periosteum stripped from the cortex with extreme ease. The brain and meninges showed nothing. Post-mortem blood cultures were sterile.

Microscopically the heart showed no change. The bones showed characteristic lesions of severe scurvy in the process of healing. Early rickets was also present, as evidenced by defects in calcification of the cartilaginous matrix substance.

DISCUSSION

We have presented the clinical histories of three infants dying unexpectedly; all of them at autopsy were found to have severe scurvy. Two of them had right-sided cardiac hypertrophy. The usual causes of sudden death in infancy, such as congenital cardiac malformation, cerebral hemorrhage, and sepsis, were absent in these children. So, too, any severe antecedent illness which might have led to diarrhea and acidosis was also lacking. Unfortunately, we do not know how much anemia was present, since blood studies were not made. We are left, then, with the question as to what role vitamin C deficiency may play in producing cardiac failure.

In adult scurvy sudden death has been recognized from early times. Lind[1] cites a passage from Lord Anson's *A Voyage Around the World* (1740-44) as follows: "Indeed the effects of this disease were, in almost every instance, wonderful. For many of our people, though confined to their hammocks, appeared to have no unconsiderable share of health; for they ate and drank heartily, were cheerful, and talked with much seeming vigour, and with a loud strong tone of voice; and yet on being the least moved, though it was only from one part of the ship to the other, and that in their hammocks, they have immediately expired. And others, who have confided in their seeming strength, and have resolved to get out of their hammocks, have died before they could well reach the deck. And it was no uncommon thing for these who could do some kind of duty, and walk the deck, to drop down dead in an instant on any endeavours to act with their utmost vigour." Again Lind says, "An uncommon degree of sloth and laziness which constantly accompanies this evil (scurvy) is often mistaken for the willful effect of the patient's natural disposition. This has proved fatal to many, some of whom, when obliged by their officers to climb up the shrouds, have been seen to expire, and fall down from the top of the mast."

In 1914 Darling[2] called attention to the presence of right-sided cardiac hypertrophy in several fatal cases of adult scurvy. He pointed out the resemblance of these hearts to those found in beriberi. A few years later Hess[3] contributed a paper on "The Cardio-Respiratory Syndrome" in infantile scurvy. This consisted of increase in the rate of pulse and respiration, together with increase in size of the base of the heart. In some electrocardiographic tracings the T-waves were unusually tall. Another important report on the relationship of scurvy and the heart in children was made by Erdheim in 1918.[4] He performed autopsies on

thirty-one scorbutic children dying in Vienna, twenty-one of whom had hypertrophy of the right ventricle. The degree of right-sided enlargement varied with the severity of the scorbutic manifestations. Aschoff and Koch[5] reported that instances of death in adults from scurvy alone were rare. However, since no fatal cases were found in their series without pulmonary edema or cardiac enlargement, these authors state that death from heart failure in scorbutic patients must be kept in mind.

In a case of experimental scurvy in an adult, Crandon and co-workers[12] noted a fall in blood pressure (from 120/70 to 90/60) after the subject had been on a vitamin C-free diet for twenty-three weeks. The pressure returned to normal when ascorbic acid was restored to the diet. Electrocardiographic tracings were normal.

We may conclude then that in the literature there is indication that vitamin C deficiency does play a role in producing changes in cardiac function. However, that vitamin C deficiency alone may not be responsible for the anatomical cardiac changes seems likely in view of their absence in many cases of severe scurvy. We have recently reviewed 32 other autopsied cases of scurvy without rickets in infants, 19 of which were classified as moderate in degree while the rest were called severe. In only 2 of the former group was there definite cardiac hypertrophy; it was present in 3 of the severe cases. These 5 children had all been ill for varying intervals before death and the cause of death was not thought to be scurvy alone. Counting the case of scurvy unassociated with rickets which was reported in this paper, one obtained an incidence of cardiac hypertrophy in only 17 per cent of these children. The possibility of vitamin B_1 deficiency in these children cannot be dismissed. Nor is the role which anemia might play at all clear.

Changes in the myocardium of scorbutic guinea pigs have been reported by numerous observers. Hojer[6] found atrophy of the muscle fibers with necrosis and calcification. Bessey and co-workers[7] noted irregular foci of fatty infiltration in the musculature. Recently attention has been drawn by Rinehart and Mettier[8] to the similarity between cardiac lesions in scorbutic guinea pigs injected with streptococci and the changes in rheumatic fever in man. Several observers[9, 10, 11] have repeated this work and in general the conclusions drawn indicate that definite changes do occur. These consist of focal hemorrhages and myocardial necroses with some proliferation of connective tissue elements. However, the lesions can be found in animals on a scorbutic diet with or without superimposed infection.

Little is known about physiologic changes in the myocardium in scurvy. As noted above, Hess saw tall T-waves in the electrocardiograms of children. However, in a case of experimental adult scurvy, Crandon and co-workers[12] noted no change in the tracings. In collaboration with Dr. Harry F. Klinefelter, Jr., we have recently begun electrocardiographic studies of scorbutic guinea pigs.

We are unable to put forward any satisfactory explanation as to why vitamin C deficiency may lead to cardiac insufficiency. It is hoped, however, that careful clinical studies in cases of severe scurvy before and after treatment may throw some light on the problem.

SUMMARY

In three cases of severe scurvy in infancy death took place suddenly and unexpectedly. Two of the children had right-sided cardiac hypertrophy. Except for this, no other changes were found to account for death. The probable importance of vitamin C deficiency in producing myocardial hypertrophy and also in leading to cardiac insufficiency is discussed. It is pointed out that vitamin C deficiency may not be the only responsible factor.

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BLOOD VOLUME AND EXERCISE

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BAZETT[1] recently has reviewed the dynamic aspects of blood volume, presenting the concept of a labile homeostatic element which readily increases or decreases to fulfill circulatory demands. The control of fluid content of the plasma appears to depend upon the relative strength of the osmotic pressure of the plasma colloids and the hydrostatic pressure of the blood in the capillaries. Important also is the more intangible factor of capillary permeability[2] and the more recently recognized factor of tissue fluid pressure.[3] The various aspects of capillary permeability have been reviewed by Landis.[4] This conception of change in blood volume depends upon the assumption that volume changes of significant degree are caused by the transit of a plasma filtrate into or out of the circulating blood by way of permeable small vessels in response to change in the balance of the factors mentioned.

Any change in blood volume brought about by means of blood depots and increased quantities of red cells thrown into circulation are believed to be of small magnitude compared with the large changes which may result from the transit of plasma filtrate. Thus, Keys and Taylor[5] point out that normal subjects exercised to exhaustion show little evidence of large splenic activity, an estimated gain of 5 to 20 c.c. of new red cells as compared with a loss from the blood of 400 c.c. of plasma filtrate containing about 1 per cent of protein.

The most important function of serum protein resides in its osmotic attraction for water, and this is the important agent in maintaining fluid balance between the blood and the intercellular tissue spaces and serous cavities.[6] The importance of protein as a physical agent in the maintenance of a normal osmotic pressure and blood volume has been emphasized by Stanbury and associates.[7]

Under certain conditions of abnormal stress, changes occur which reduce the plasma volume; but such reduction causes an increase in the plasma protein concentration and tends to prevent undue loss of fluid from the plasma. Such an instance occurs with exercise, when the plasma volume is diminished by loss of plasma filtrate and the concentration of plasma protein is considerably increased. Keys and Taylor,[5] however, report that while the serum protein concentration increases, the actual measurable osmotic pressure decreases, and they believe that this decrease is directly related to a change in the mean size of the protein molecule. Under the condition of vigorous exercise, an added

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mechanism which tends to increase the colloidal osmotic pressure in support of the blood volume has been studied by Keys and Adelson.[8] This mechanism is the increase in serum calcium which is found to parallel closely the increase in the concentration of plasma protein following vigorous exercise. "Diffusible" calcium is restrained from diffusion to the same extent that plasma proteins are restrained and will be osmotically active, resulting in a net increase in osmotic pressure estimated at 30 to 60 mm. of water.

Our interest in the problem of the changes in blood volume in relation to exercise was aroused when this factor was considered as a possible explanation for the brief episodes of a shocklike nature sometimes occurring in subjects who had exercised vigorously on the bicycle ergometer or on the treadmill during studies previously reported.[9, 10] These episodes consisted of circulatory collapse with pallor, weakness, nausea, giddiness, fall of blood pressure, and sometimes syncope and loss of consciousness. They usually occurred within a brief period after the end of exercise, during the recovery period. The subject at the onset of such an episode was seated upright in a chair with a back and was relaxed and at ease. These "reactions" could sometimes be aborted by having the subject lean far forward, but at other times a few minutes in the recumbent position was necessary for recovery of the blood pressure. On some occasions full syncope occurred before such restorative efforts could be instituted.

We have therefore reviewed our figures relating to blood volume in our studies of the physiology of exercise in children to determine the relation (1) of blood and plasma volume to exercise, and (2) of blood and plasma volume to the shocklike episodes occasionally encountered.

DESCRIPTION OF THE EXPERIMENTS AND METHODS

The subjects were healthy boys 10 to 17 years of age. In twenty-nine experiments the boy exercised on the bicycle ergometer; the degree of exercise is referred to as moderate or vigorous. This experiment has been described previously.[10] In fifty-six experiments the boy exercised on the treadmill, the uniform exercise used in each instance, consisting of a walk for fifteen minutes at 3.5 miles per hour and up an 8.6 per cent grade, referred to as moderate exercise, and a run up the same grade at 6 or 7 miles per hour for as long as the subject was willing or able, referred to as vigorous exercise. The duration of this run was usually 2 to 4 minutes, although in some instances subjects of unusual stamina ran five minutes without exhaustion, in which case the experiment was sometimes repeated with a speed of 8 miles per hour.

In nineteen instances changes in the plasma volume during exercise have been determined by changes in the concentration of the blue dye, T-1824, in the plasma following a single injection of the dye, according to the "indirect" method described by Gibson and Evans.[11] The dye

concentration in the plasma was determined in the photoelectric colorimeter according to the method of Gibson and Evelyn.[12] In the majority of cases, however, the decrease in the plasma volume has been calculated from the rise in plasma protein concentration on the assumption that loss of water from the plasma is the only factor which affects the protein concentration appreciably during a short period of exercise. Changes in blood volume have also been calculated, using hematocrit data in combination with changes in plasma protein concentrations. Plasma protein concentrations were estimated from total nitrogen analysis by means of the factor 6.25. The total nitrogen was determined on 0.1 c.c. samples by the micro-Kjeldahl method of Pregl[13] and was corrected for nonprotein nitrogen. Cell volume determinations were made in calibrated small test tubes containing 4 to 5 c.c. of heparinized blood after centrifuging for one hour.

All of the experiments were conducted in the morning, the boy presumably having had no food since the previous evening meal. The resting sample was drawn after the boy had reclined in bed for at least thirty minutes, the sample for moderate exercise was drawn during the twelfth minute of exercise, while exercise continued, and the sample for vigorous exercise was drawn five minutes after exercise ceased. The five-minute recovery period after exercise was allowed for maximum diffusion of lactic acid from the tissues into the blood which was required for other studies. Since changes in plasma protein are governed by quite different forces from those affecting lactic acid, it is possible that the concentrations measured do not represent concentrations existing at the end of the run. It is possible, therefore, that the plasma volume changes we have calculated for vigorous exercise may be slightly low.

Blood samples were drawn with as little stasis as possible. Ordinarily the vein was constricted by hand pressure long enough to insert the needle, and the pressure then was released.

RESULTS

Table I shows the results obtained after exercise on the bicycle ergometer; Table II, those after exercise on the treadmill. The tables include data on both white and negro boys. The systolic and diastolic blood pressures measured as soon as possible after exercise ceased (usually between 30 and 60 seconds) are also included. The duration of the vigorous exercise is indicated in the right hand column.

It is apparent that the decrease in plasma and blood volumes as calculated from the increased protein concentration and hematocrit readings shows great individual variation, even with the performance of a fixed task, such as the fifteen-minute walk on the treadmill at the standard rate. Referring to Table II, it is seen that in fifty-three individuals the decrease in plasma volume has varied from 4.6 per cent to 15.2 per cent and the decrease in blood volume, from 0 to 11.9 per cent. Although

TABLE I

CHANGES IN PLASMA[1] AND BLOOD[2] VOLUME AND IN BLOOD PRESSURE DUE TO EXERCISE ON A BICYCLE ERGOMETER

DATE	SUBJECT	AGE		PER CENT DECREASE IN PLASMA VOLUME		PER CENT DECREASE IN BLOOD VOLUME		SYSTOLIC[3] BLOOD PRESSURE		DIASTOLIC[3] BLOOD PRESSURE		DURATION	
		YR.	MO.	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MIN.	SEC.
White Boys, Vigorous Exercise for One Minute													
11/21/38	L. S.	11	3	−3.7	−5.0	−2.8	0.0	145	145	89	63	1	0
11/21/38	J. B.	12	2	−2.8	−5.1	−1.4	−0.7	142	146	66	58	1	0
11/21/38	W. P.	13	11	−3.6	−4.8	−2.6	−0.2	148	157	79	83	1	0
1/ 9/39	D. A.	11	5	−5.2	−6.4	−2.8	−1.1	133	132	49	48	1	0
1/16/39	P. P.	11	4	−6.0	−6.1	−2.5	−1.7	160	176	76	90	1	0
1/16/39	F. C.	12	11	−3.6	−6.1	−0.4	−0.6	150	174	71	88	1	0
Average		12	2	−4.2	−5.9	−2.1	−0.7	146	155	72	72	1	0
White Boys, Vigorous Exercise for Five Minutes													
2/22/40	F. C.	13	11	−8.6	−22.8	−1.6	−15.0	150	158	70	50	5	0
2/26/40	H. K.	13	11	−6.3	−08.6	−7.4	−06.7	110	142	72	80	5	0
2/29/40	B. W.	13	8	−5.5	−09.1	+0.6	−03.8	134	136	68	55	5	0
Average		13	10	−6.8	−13.5	−3.2	−08.5	131	145	70	62	5	0
Negro Boys, Younger Group													
2/27/39	R. W.	13	9	−1.6	−1.4	−1.8	−2.5	157	189	78	75	1	0
3/ 6/39	R. H.	12	6	−3.8	−5.3	−2.4	+0.8	115	120	47	53	1	0
3/27/39	J. B.	11	8	−4.9	−1.9	−5.1	−1.7	121	125	71	57	1	0
3/30/39	R. B.	11	6	−5.2	−6.7	−1.4	−2.2	134	148	57	86	1	0
7/14/39	J. F.	12	8	−2.8	−6.0			130	124	90	80	1	0
7/19/39	H. M.	13	9	−7.4	−8.2	Hematocrit data not		132	124	88	60	1	10
8/11/39	T. S.	14	4	−8.7	−5.2	available		134	150	84	55	2	0
8/25/39	H. N.	15	7	−5.8	–			136	136	80	84	0	50
Average		13	2	−5.0	−5.0	−2.7	−1.4	132	140	74	69	1	8
Negro Boys, Older Group													
7/26/39	H. G.	16	0	+4.7	−7.7			122	142	84	80	3	20
8/ 4/39	N. W.	17	0	−4.2	−8.8	Hematocrit data not		138	160	82	60	1	30
8/ 4/39	H. H.	17	0	+0.8	−3.6	available		156	148	72	70	1	0
8/11/39	J. M.	17	4	−4.2	−6.9			132	156	68	56	1	25
8/21/39	C. H.	17	8	−8.8	−8.9			138	144	78	88	1	5
8/30/39	A. B.	16	4	−4.4	−6.9			142	158	88	78	1	40
Average		16	10	−2.7	−7.1			138	151	79	72	1	40

[1]Changes in plasma volume are estimated from the determined changes in plasma protein concentration.
[2]Changes in blood volume are estimated from changes in plasma and cell volumes.
[3]First blood pressure reading after exercise.

TABLE II

CHANGES IN PLASMA[1] AND BLOOD[2] VOLUME AND IN BLOOD PRESSURE DUE TO EXERCISE ON A TREADMILL

DATE	SUBJECT	AGE		PER CENT DECREASE IN PLASMA VOLUME		PER CENT DECREASE IN BLOOD VOLUME		SYSTOLIC[3] BLOOD PRESSURE		DIASTOLIC[3] BLOOD PRESSURE		DURATION OF RUN	
		YR.	MO.	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MIN.	SEC.
White boys who ran at 6 miles an Hour													
5/ 6/40	R. T.	13	0	−06.6	−12.8	−04.8	−07.3	120	120	80	75	3	50
5/13/40	T. W.	13	3	−07.2	–	−04.9	–	140	–	96	–		
5/16/40	J. C.	12	4	−08.1	−08.0	–	–	140	155	94	82	4	8
6/27/40	J. M.	13	2	−13.3	−10.0	−10.8	−07.4	160	170	72	64	3	0
7/31/40	B. W.	14	1	−09.7	−14.1	−08.0	−05.8	130	150	70	78	2	45
7/31/40	G. W.	13	2	−10.8	−11.2	−05.0	−03.0	110	120	80	84	1	5
8/12/40	J. A.	13	5	−09.9	−14.6	−04.7	−04.8	122	150	84	90	5	0
10/ 7/40	L. B.	12	6	−08.0	−14.7	−06.0	−10.0	146	165	62	68	1	15
10/17/40	J. W.	11	7	−07.4	−09.4	−03.6	−02.2	128	148	72	96	1	0
3/24/41	J. B.	11	11	–	−06.3	–	−00.4	130	150	70	88	2	5
6/23/41	D. K.	11	3	–	−11.0	–	−06.4	100	130	60	65	3	34
Average		12	8	−09.0	−11.2	−06.0	−05.3	130	146	76	79	2	46
White boys who ran at 7 miles an Hour													
4/18/40	J. A.	13	1	−07.9	−06.0	−06.2	+02.6	126	140	80	88	1	25
5/ 2/40	L. W.	16	6	−08.4	−08.4	–	−02.8	146	195	86	55	6	0
6/ 6/40	P. M.	15	5	−12.4	−17.6	−04.4	−11.9	155	180	50	45	3	50
7/18/40	T. P.	13	11	−08.3	−13.1	−05.1	−08.4	142	148	78	92	3	50
7/25/40	N. G.	16	1	−05.8	−17.6	−07.4	−12.2	148	150	74	60	2	22
7/29/40	W. Y.	14	9	−10.3	−15.9	–	−09.5	146	190	84	30	4	54
8/ 1/40	T. A.	15	6	−12.8	−16.2	−09.3	−07.7	156	150	96	75	5	0
8/ 2/40	F. C.	14	4	−12.1	−16.6	−09.5	−10.5	145	160	62	60	1	35
8/ 7/40	R. S.	14	10	−06.2	−11.3	–	–	138	140	80	70	4	55
8/ 7/40	H. K.	14	5	−09.3	−13.7	−04.6	−07.9	142	146	90	90	2	10
8/10/40	L. Z.	15	1	−05.4	−11.4	−03.1	−07.6	138	200	62	80	5	0
8/14/40	R. T.	13	3	−04.7	−07.9	−05.2	−07.4	140	136	80	78	2	14
8/14/40	E. B.	14	3	−13.1	−14.9	−04.7	−05.0	130	190	92	80	5	0

10/10/40	M. D.	14	6	−07.4	−12.9	−04.0	−03.3	145	154	76	66	3	15
10/14/40	R. G.	14	10	−08.6	−10.6	−04.2	−05.2	132	156	72	78	2	0
10/31/40	H. W.	14	1	−09.4	−09.8	−11.9	−07.2	128	128	68	62	1	15
11/ 4/40	G. H.	14	4	−14.1	−12.4	−06.4	−04.6	130	155	60	66	1	15
11/25/40	J. D.	16	7	−11.0	−14.1	−03.0	−09.0	118	160	82	76	2	0
11/28/40	A. D.	14	1	−15.2	−12.4	−09.4	−09.8	134	150	78	60	2	0
12/ 2/40	W. W.	16	10	−09.5	−18.7	−03.0	−05.7	148	178	80	70	4	8
12/ 5/40	E. H.	16	9	−07.4	−10.8	00.0	−03.0	142	154	72	70	3	0
12/12/40	V. H.	16	1	−09.4	−12.4	−05.0	−06.2	128	160	62	82	3	0
1/16/41	R. O.	15	7	−05.2	−08.1	−01.2	−03.4	145	165	80	55	5	0
1/16/41	B. B.	16	2	−10.2	−11.0	−06.8	–	148	165	75	60	5	0
1/20/41	J. J.	16	2	−09.7	−08.4	–	–	120	150	70	60	2	12
1/21/41	R. deG.	16	0	−14.0	−14.3	−03.3	−03.8	134	150	80	65	2	30
3/17/41	D. P.	15	3	−10.2	−07.5	−09.6	−06.2	110	170	76	76	3	10
3/17/41	H. N.	13	3	−08.4	−09.2	−02.0	−07.5	130	168	80	85	2	20
3/31/41	B. S.	16	4	−04.6	−06.3	−01.6	00.0	150	150	70	50	2	45
4/28/41	W. D.	16	5	−12.2	−12.2	−07.3	−03.5	152	166	64	60	1	57
5/29/41	W. R.	16	2	−09.7	−12.2	−02.4	−08.1	140	160	85	70	2	30
5/29/41	J. R.	16	5	−09.2	−11.1	−05.3	−10.4	135	155	80	90	1	52
Average		15	3	−09.4	−12.0	−05.2	−06.4	138	160	76	70	3	6
Negro boys who ran at 7 miles an Hour													
2/27/41	R. Sc.	17	8	−11.9	−13.5	−07.8	−07.2	155	200	60	0	5	0
2/27/41	T. G.	16	9	−08.8	−14.4	−04.5	−09.2	140	130	80	50	3	30
3/ 3/41	J. W.	16	3	−07.0	−10.7	0.0	−03.9	110	140	60	68	2	3
7/ 3/41	H. M.	16	9	−08.4	−09.5	−02.8	−07.2	160	180	90	70	2	5
3/20/41	E. R.	16	9	−06.4	−08.6	−03.4	−07.0	140	180	72	50	5	0
3/27/41	S. S.	18	0	–	−09.5	–	−04.7	140	160	62	70	1	50
4/10/41	C. B.	16	9	−07.9	−05.8	−08.7	00.0	140	185	70	65	1	47
6/27/41	J. P.	16	9	−14.7	−16.9	−09.6	−07.5	130	130	90	60	5	0
8/15/41	L. T.	16	8	−10.8	−10.5	−05.2	–	158	180	88	90	2	19
8/15/41	H. T.	15	4	−12.7	−11.7	−09.9	−04.4	122	146	68	80	3	20
Average		16	9	−09.8	−11.1	−05.8	−05.7	140	161	74	60	3	11

[1]Changes in plasma volume are estimated from the determined changes in plasma protein concentration.
[2]Changes in blood volume are estimated from changes in plasma and cell volumes.
[3]First blood pressure reading after exercise.

the magnitude of the changes has been considerably less, there has been similar variation in reduction of blood and plasma volumes in the standard moderate exercise on the bicycle, 4.7 to 8.8 per cent for plasma volume and 0.6 to 7.4 per cent for blood volume. Determination of oxygen consumption during exercise has shown that the work done in moderate exercise on the bicycle is somewhat less than that on the treadmill, an average of 18.4 c.c. per kilogram per minute as compared with 26.7 c.c. per kilogram per minute.

After vigorous exercise, either on the bicycle or the treadmill, the plasma volume diminution in a given individual is usually much greater than the change after moderate exercise. Some of this difference probably can be explained by the fact that recovery of volume by re-entrance of fluid into the plasma from the tissue fluid compartment is not complete in the rest period of ten minutes allowed between moderate and vigorous exercise, and that consequently the base line is lower at the start. To what extent this accounts for the difference, and to what extent the more exhaustive work is responsible, we are unable to say.

In Table III results using the dye method are compared with those depending on changes in plasma protein concentration. Changes in plasma volume determined by the latter method do not show good agreement with those determined simultaneously by estimation of the changes in concentration of the injected blue dye, T-1824. The dye method has usually given higher values, frequently more than double those obtained by the plasma protein method. Ebert and Stead[14] recently have reported a similar discrepancy. Initial pre-exercise blood volume determinations on many children, using the blue dye, T-1824, have given us experience and thorough familiarity with the method. As a determination we have found it far less accurate than the plasma protein determination.

The determination of plasma volume after exercise depends upon a comparison of the dye concentration actually found with that assumed to exist at that moment under basal conditions as calculated from the disappearance slope of the dye. A slight error in estimating the disappearance slope may introduce a large error when a period of three hours has elapsed after the injection of the dye before the exercise sample is taken, as was the case in our experiments. Another source of error in the dye method has been described by Ebert and Stead[14] who have shown that errors due to changes in the optical properties of the dye-free plasma during exercise may account for as much as 40 per cent of the apparent increase in dye concentration. Kaltreider and Meneely[15] found a better correspondence between changes in blood volume during exercise as calculated from changes in plasma protein and those obtained by the dye method. In their experiments a much shorter time elapsed between the injection of the dye and the exercise period.

TABLE III

COMPARISON OF CHANGES IN BLOOD VOLUME AS MEASURED SIMULTANEOUSLY BY CHANGES IN PLASMA PROTEIN CONCENTRATION AND BY INJECTED BLUE DYE, T-1824

DATE	SUBJECT	AGE		PER CENT DECREASE IN PLASMA VOLUME			
				MODERATE EXERCISE		VIGOROUS EXERCISE	
		YR.	MO.	MEASURED BY PROTEIN DETERMINATION	MEASURED BY DYE CONCENTRATION	MEASURED BY PROTEIN DETERMINATION	MEASURED BY DYE CONCENTRATION
Exercise on Bicycle							
7/19/39	H. M.	13	9	−07.4	–	−08.3	−09.5
8/11/39	T. S.	14	4	−08.7	−10.6	−05.2	−06.3
8/11/39	J. M.	17	4	−04.2	−14.0	−06.8	−14.4
8/16/39	S. S.	17	2	−07.2	−02.3	−12.7	−12.1
8/23/39	S. Sc.	16	11	−06.8	−15.4	−11.4	−18.7
8/25/39	H. N.	15	7	−05.8	−07.4	–	–
8/30/39	A. B.	16	4	−04.4	−12.9	−06.9	−17.3
Average		15	11	−06.4	−10.4	−08.6	−13.0
Exercise on Treadmill							
10/ 7/40	L. B.	12	6	−08.0	−17.1	−14.7	−18.9
10/10/40	M. D.	14	6	−07.4	−14.1	−12.9	−17.6
10/14/40	R. G.	14	10	−08.6	−08.2	−10.6	−15.8
11/14/40	J. Y.	Adult		−14.8	−13.9	−17.2	−16.0
11/28/40	A. D.	14	1	−15.2	−12.3	−12.4	−09.1
12/ 5/40	E. H.	16	9	−07.4	−13.6	−10.8	−19.1
12/12/40	V. H.	16	1	−09.4	−14.4	−12.4	−12.1
1/30/41	B. B.	16	2	−09.5	−09.7	−11.6	−14.8
2/17/41	R. O.	15	7	−09.4	−14.0	−10.2	−19.8
3/ 6/41	R. Sc.	17	8	−12.7	−17.9	−15.3	−22.8
4/ 3/41	J. W.	16	3	−05.0	−10.8	−08.4	−17.0
4/23/41	W. D.	16	5	−12.2	−08.8	−12.2	−13.1
Average		15	5	−10.0	−12.9	−12.4	−16.3

A typical response of the circulation to exercise is shown in Fig. 1. This demonstrates the magnitude of the strain imposed upon the circulation by vigorous exercise. The pulse rate reaches 190 to 200, as recorded during exercise by the cardiotachometer. Likewise the blood pressure is markedly elevated on the systolic side, while the diastolic pressure is usually slightly or moderately diminished, the pulse pressure being greatly increased. The blood pressures have been recorded only after completion of the test and during recovery, and while only a short time elapses between the end of the run and the first recording of pressure, it is probable that the peak of the pressure is not shown. The usual response during recovery is a rather rapid fall of the systolic pressure to the resting value and the gradual increase of the diastolic pressure to the normal level. While this response is usual, variations may occur individually, both in the degree of elevation and in the shape of the recovery curve. Rarely, the diastolic end point is not recognizable and the diastolic pressure is recorded as 0, resulting in a pulse pressure of great magnitude, as for instance, 200 mm. of mercury. Such marked distortion of the normal hydrostatic pressure, however, is not necessary to produce blood volume changes of considerable degree, as shown by comparing the blood pressure readings after the walk with the respective protein changes.

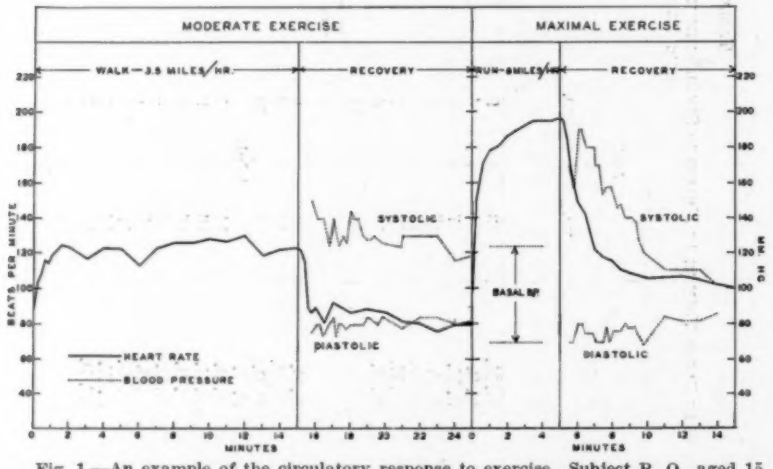

Fig. 1.—An example of the circulatory response to exercise. Subject R. O., aged 15 years, April 7, 1941. The heart rate was recorded by a cardiotachometer during and for ten minutes following exercise. Blood pressures were determined by a mercury sphygmomanometer at frequent intervals for ten minutes following exercise.

In Table IV the subjects showing evidence of circulatory collapse or clinical evidence of shock are grouped together. There are no uniform objective findings. While syncope usually occurred in those instances in which the blood pressure had dropped to the shock level, this was not

TABLE IV

CHANGES IN PLASMA[1] AND BLOOD[2] VOLUMES AND IN BLOOD PRESSURE DUE TO EXERCISE IN BOYS WHO HAVE SHOWN A SHOCKLIKE REACTION AFTER VIGOROUS EXERCISE

DATE	SUBJECT	AGE		PER CENT DECREASE IN PLASMA VOLUME		PER CENT DECREASE IN BLOOD VOLUME		SYSTOLIC[3] BLOOD PRESSURE		DIASTOLIC[3] BLOOD PRESSURE		DURATION OF RUN	
		YR.	MO.	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MODERATE EXERCISE	VIGOROUS EXERCISE	MIN.	SEC.
Bicycle													
7/28/39	L. B.	16	6	–04.6	–06.3			134	130	82	82	0	20
8/16/39	S. So.	17	2	–07.2	–12.8			134	170	80	80	4	0
8/23/39	S. Sc.	16	11	–06.9	–11.2	Hematocrit data		130	158	72	60	1	0
2/19/40	J. G.	Adult		–08.2	–15.2	not available		118	140	76	78	5	0
2/26/40	R. S.	14	4	–07.6	–10.9			130	134	84	50	5	0
3/25/40	N. W.	14	9	–08.8	–15.6			140	124	82	50	5	0
Average				–07.2	–12.0			131	143	79	67	3	23
Treadmill													
11/14/40	J. Y.	Adult		–14.8	–17.2	–06.7	–05.8	125	115	80	65	2	43
3/31/40	J. Co.	17	0	–09.3	–10.7	–08.4	–05.7	92	94	54	40	1	40
12/ 9/40	N. B.	14	7	–08.1	–09.7	–04.1	–03.4	138	118	88	60	1	47
Average				–10.7	–12.5	–06.4	–05.0	118	109	74	55	2	03

[1]Changes in plasma volume are estimated from the determined changes in plasma protein concentration.
[2]Changes in blood volume are estimated from changes in plasma and cell volumes.
[3]First blood pressure reading after exercise.

always the case. In one case the subject fainted when the blood pressure level was 136/74; in another instance, at 116/84.

Likewise, it is seen that the subjects in this group who reacted to exercise in an abnormal manner showed no uniformity in blood volume diminution. Those having the greatest diminution of volume are not the ones showing evidence of circulatory collapse.

Of particular interest are the three subjects who did not have any appreciable elevation of blood pressure or pulse pressure following exercise. These subjects collapsed during the recovery period following exercise; their volume changes, while definite, were not spectacular. It seems probable that this abnormal group did not have shock, due to low blood volume, and we are unable to explain the mechanism of collapse on this basis.

DISCUSSION

Kaltreider and Meneely[15] have reviewed the literature relating to the effect of exercise on the volume of the blood. They found that studies previous to theirs "have indicated that as a result of exercise there is an increase in the concentration of red blood cells and hemoglobin." It was suggested that red blood cells were extruded from blood depots or that there was a change in the concentration of blood due to passage of fluid from blood to tissues. They found no unanimity of opinion relative to blood volume during and after exercise, since observers found in dogs and in man, either increases or decreases in volume.

In seven normal subjects these authors found, using the blue dye, T-1824, a prompt and definite decrease in plasma volume in every instance with elevation of arterial and venous pressures but with no correlation between increase in pressure and decrease in volume. They found the changes in cell volume to be variable and slight.

Our findings are in accord with these observations. There has been in almost every instance a definite increase in the protein concentration in the serum, which is considered to represent inversely a diminution of plasma volume, since there is no known depot for plasma proteins and since the leakage of protein from the blood in the plasma filtrate is negligible. Determinations of the blood volume following both moderate and vigorous exercise by the use of the indirect dye method in eighteen experiments have shown an even greater diminution of blood volume than would be indicated by estimation from changes in the serum protein alone.

It is also seen that while the diminution of plasma volume is of a definite and perhaps significant degree in those subjects having symptoms or signs of shock or circulatory collapse, this cannot be the only factor, since in other instances there have been decreases of equal or greater magnitude with no circulatory or clinical changes comparable. It is impossible to say, since in some children there is a marked emotional

factor, whether there is at the time simple vagal syncope, or ordinary fainting. However, these abnormal reactions to exercise occur uniformly after exercise, never before, and usually directly afterward. We believe that low blood volume is at least a factor in instances of collapse after exercise and that it may play a role in the reactions frequently seen in strenuous competitive athletics.

We further suggest, although we have no direct evidence, that rapid fall in blood pressure during the recovery period with rapid diminution of vasomotor tone may occur at a rate in excess of the restoration of the plasma filtrate and blood volume, and that consequently a relative blood volume deficiency may, in some instances, result in the abnormal reactions previously described.

Although blood sugar levels are not shown in the protocols, such determinations were done, and hypoglycemia is not found following the periods of exercise used in these observations.

SUMMARY

1. The increase of serum protein concentration has been determined following both moderate and vigorous exercise in experiments on eighty-five healthy boys. The blood pressure changes have also been observed.

2. In nineteen of these subjects, the increase of the concentration of the blue dye, T-1824, following exercise has also been determined.

3. In twelve of these subjects there was evidence of circulatory collapse.

CONCLUSIONS

1. There is in most cases an increase in the concentration of the serum proteins following exercise, and in the concentration of the blue dye, T-1824, where this has been previously administered.

2. These observations are considered to be evidence of the diminution of the plasma volume, and hence the blood volume, following exercise, and it is believed that this is the usual response to exercise.

3. In instances of circulatory collapse following exercise, there is no good correlation between the diminution of blood volume and the reactions observed, instances being observed of marked lowering of blood volume without circulatory collapse. It is concluded that, while this factor may reasonably be presumed to play a part in collapse following exercise, other causes must be contributory.

The authors are indebted to Miss Leona Woods and Mr. Harold Ziskin for assistance in the experimental work.

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INFANTILE ACNE VULGARIS

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ACNE vulgaris is a disorder manifested by large or small papules, papulopustules, nodules, and comedones that is caused primarily by an infection of the pilosebaceous glands of the skin with acne bacillus and *Staphylococcus albus*. Acne vulgaris is present usually during the periods of puberty and adolescence when the glands of the body are developing and are overactive, but a small percentage of cases begin before the eleventh year. It is accepted almost universally that acne vulgaris is of endocrine origin, but other contributing and aggravating factors, such as constipation, faulty hygiene, irrational diet, and undernutrition, often are associated with it. The bacteria found are secondary invaders in a soil of oil or comedones, which result either from excessive or defective activity of the sebaceous glands. At any rate, it appears that the endocrine changes at puberty and adolescence affect the pilosebaceous apparatus.

Current textbooks and occasional papers in the literature note the rare occurrence of acne in infancy. The report of a few cases in infants is of interest not only because of its rarity, but also because of the bearing it may have on the etiology. This does not argue against the endocrinous origin of acne, since manifestations of glandular hyperfunction, such as mastitis neonatorum and seborrhea of the scalp, are found in early infancy.

Beatty and Bigger[1] reported a case in a 6-month-old male infant with acne of the cheeks. Bacteriologic investigation disclosed acne bacillus and *Staph. albus*. Ayres[2] reported three cases in male infants. Gray[3] reported a typical case of acne vulgaris in a female child aged 2 years. In a personal communication Sulzberger[4] noted the rare occurrence of the condition in infancy.

The two cases reported below were seen within a period of eight months.

CASE REPORTS

CASE 1.—E. L. M., a male child, presented a dryness of the cheeks at the age of 1 month. The use of boric ointment cleared up this condition within ten days. At the age of 3 months, when the child was seen again, the skin of both cheeks was involved thickly with comedones, papules, and pustules as seen in typical acne vulgaris. Dr. William Garbe, a dermatologist, confirmed the diagnosis. Therapy consisted of soap and warm water washes with a skin brush and the application of a half-strength solution of lotio alba. The condition improved progressively until at 8 months the skin was entirely normal except for small pitted scars, which resulted from the healing of the pustules that followed the comedones.

The lesion was considered at first to be a mild eczema, but it did not respond to elimination of possible allergens, and at 3 months the diagnosis was apparent. The health of the child was perfect otherwise. Continued observation over a period of two years failed to show any further comedones or pustules. There were no hereditary factors. Only mineral oil had been used on the skin previously.

CASE 2.—B. L., a male child aged 1 month, presented pustules on both cheeks which responded rapidly to the application of 2½ per cent ammoniated mercury ointment. At 3 months, definite comedones and pustular acne were present on both cheeks. Dr. Garbe again confirmed the diagnosis of infantile acne vulgaris. Under therapy, as noted in the previous case, at the age of 7 months there were no further comedones or pustules noted. Small pitted scars remained. This child was a normal breast-fed infant with a normal family history. After a twelve-month period of observation, no further comedones or acneform lesions had appeared.

Fig. 1.—Photograph showing acne lesion of the cheek in infant 8 months of age (Case 2).

COMMENT

During the latter months of intrauterine life,[5] there is a marked stimulation of the epithelium, and particularly of the hair bulb and sebaceous glands, which leads to the formation of the vernix caseosa and the lanugo hair of the fetus. This hyperactivity ceases with birth and both the vernix caseosa and the physiologic hyperkeratosis of the newborn disappear at birth. The stimulation of the fetal pilosebaceous apparatus occurs at the time when the maternal, and probably fetal, circulation contains the highest level of sexual hormones (e.g., prolans, estrin). Ordinarily this hyperactivity ceases at birth and is not resumed until puberty, when the individual produces his own sexual hormones. The stimulation of the pilosebaceous apparatus probably depends directly or indirectly on the hormones and so may help explain acne

vulgaris of adolescence. In the cases reported here and elsewhere it may be produced by a carry-over from fetal life, as most cases seem to clear up in about six to nine months. The ordinary therapeutic procedures employed probably hasten the development of the pustule from the comedone and then healing occurs.[5]

In both these infants, after a period of twelve to eighteen months of observation, no further comedones have developed. It also brings up the question about the indiscriminate use of oils and ointments on the skin which probably occludes the facial glands, leading to the formation of comedones and subsequent acneform eruptions. However, it was not until the age of 3 months that definite comedones formed. In both cases, water and soap were discontinued on account of the skin dryness. Mineral oil only was used. This suggests a possible interference with the proper function of the pilosebaceous apparatus of the face with subsequent development of comedones and acne.[5]

SUMMARY

Two cases of acne vulgaris in infants under the age of 1 year are reported. In both instances soap and water were discontinued on account of dryness of the skin, and bland mineral oil was used. This may have been a factor in the causation of subsequent acne. The etiology of the condition is discussed. A photograph of the lesion in Case 2 is shown.

Since this paper was written, two additional instances of the same condition have been observed by me during the past three months.

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TULAREMIA WITH LOCAL LESIONS CONFINED TO THE TONSILS

A Case Report

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TULAREMIA with local manifestations of the disease confined to the tonsils and pharynx would seem to be uncommon. We were able to find only four recorded cases in the literature of this disease.[1, 2, 3, 4] It would seem advisable, therefore, to record a fifth case in which the lesions were confined entirely to the tonsils.

A 6-year-old white girl was admitted to the University of Virginia Hospital on Aug. 21, 1941, with the complaint of fever, headache, sore throat, and general malaise of four weeks' duration. The first day of her illness can be dated as of July 25, 1941, at which time she complained of headache and some nausea. On the following day she appeared unduly fretful, and elevation of temperature was noted. On the third day of illness she was seen by her family physician who prescribed treatment. Her illness progressed and soreness of the throat became more marked. At this time she was seen by a second physician who administered sulfanilamide because of what appeared to be an obvious tonsillitis. She was treated at home for a period of days with no improvement and was then taken to a neighboring hospital where she remained for about a period of ten days. While at this hospital her general appearance was strongly suggestive of typhoid fever except for the unusual appearance of the tonsils. The tonsils were markedly inflamed and swollen and were almost meeting in the middline, with the crypts filled with exudate. Over a period of days the lesions in the throat showed no tendency to heal and the appearance at this time was not unlike that sometimes observed in blood dyscrasias. While in this hospital the child continued to remain acutely ill. There was marked anorexia and at times delirium.

Laboratory findings at this time were as follows: red cell count, 2,440,000; white cell count, 10,400; Hemoglobin, 40 per cent (Dare). The differential count was as follows: bands, 14 per cent; segmented, 58 per cent; small mononuclear, 19 per cent; large mononuclear, 2 per cent; transitionals, 7 per cent. Throat culture showed diplococci and occasional pneumococci and was negative for diphtheria and Vincent's infection. Blood cultures and stool cultures were negative for typhoid fever. Urinalysis was negative.

On admission to the University of Virginia Hospital physical examination revealed a pale, listless, irritable, and severely ill white child. The skin showed a slight yellowish tinge and the mucous membranes were pale. The breath was foul. Examination of the eyes and ears showed no abnormality. The throat and tonsils were markedly inflamed with the tonsils practically meeting in the midline. The tonsillar crypts contained a large amount of caseous material. The cervical glands were moderately swollen and tender. Examination of the chest, heart, and abdomen was negative. The spine showed no stiffness or tenderness. The genitals and lower extremities showed no abnormalities.

Laboratory data at the time of this admission were as follows: red cell count, 2,400,000; white cell count, 10,400; hemoglobin, 40 per cent (Dare). The smear

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showed the following: band cells, 14 per cent; segmented, 58 per cent; mononuclear, 21 per cent; transitionals, 7 per cent. Anisocytosis was fairly marked and toxic granulation of the white cells was noticed. Platelets were within the limits of normal. Wassermann and Kahn tests were negative. Throat culture revealed a few pneumococci and was negative for Vincent's infection and diphtheria. Blood cultures on two occasions were negative for typhoid fever and other organisms. Widal test was negative. Urinalysis was within the limits of normal.

The course of the illness continued to be that of sepsis, and repeated blood transfusions were necessary.

Fig. 1.—Appearance of tonsil during seventh week of illness, showing marked hypertrophy and exudate still present.

Further history revealed that several days before onset of illness the child had helped to skin several rabbits. Because of this history, agglutination tests for tularemia were performed and were found to be positive in dilutions up to 1:1,260, thus establishing the diagnosis of tularemia.

Convalescence was slow but steady and the child was discharged from the hospital well on the road to recovery thirty-five days after onset of illness.

SUMMARY

A case of tularemia with the local lesions confined to the tonsils is reported. The lesions of the tonsils were characterized by a slight tendency toward healing with the picture not unlike that seen at times in certain blood dyscrasias.

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MEDITERRANEAN (COOLEY'S) ANEMIA IN A YOUTH OF NINETEEN YEARS OBSERVED SINCE EARLY CHILDHOOD

Familial Aspects and Hematologic Features of the "Carrier" or Asymptomatic Case

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THE separation of erythroblastic anemia from the miscellaneous group of von Jaksch's anemia by Cooley brought to light many children suffering with this disease. As a result of his publications, patients with this type of anemia have been readily recognized and frequently reported. Attention usually has been attracted to the severe form of the disease with an onset in early infancy, characterized by rapid progression and by a fatal outcome usually antedating puberty. Temporary remissions may be induced by frequently repeated transfusions and occasionally by splenectomy.

There is a milder form of the disease which usually passes unrecognized until after the period of infancy and which is probably more widespread and in which the outlook appears more favorable. Recent studies have revealed familial and hereditary aspects of this disease and the presence in one or both parents and in the healthy offspring of unsuspected blood and skeletal abnormalities. Because of the possibility of transmission of the disease by these individuals, the detection of these so-called carriers assumes increased significance.

The case to be reported is that of a youth of 19 years with Mediterranean anemia who has been under observation since he was 4 years of age. He illustrates the form of the disease in which adult life is reached. The case emphasizes the familial features of the disease, since every member of the family revealed hematologic abnormalities of varying degree.

CASE REPORT

D. M. was first observed at the New York Nursery and Child's Hospital on Nov. 27, 1926, at the age of 4 years with the complaint of increasing anorexia and listlessness. He was born in New York on Aug. 13, 1922, of Sicilian parents. The patient showed a yellowish pallor, the cervical lymph nodes were palpable, the lungs were normal, and a loud systolic murmur was heard over the entire precordium. The liver was felt two fingerbreadths and the spleen one fingerbreadth below the costal margin. Blood studies on admission (Table I) showed a hemoglobin of 8.5 Gm. per 100 c.c. of blood and a red blood cell count of 3,700,000 per cubic millimeter, with moderate anisocytosis, poikilocytosis, 3 nucleated red blood cells to 100 white blood cells, and 11 per cent reticulocytes. He received 300 c.c. of blood and was discharged from the hospital on Dec. 9, 1926.

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Following this discharge and until April, 1929, the patient was readmitted five times and in two of these admissions the anemia was sufficiently severe to require further transfusions. A summary of the more important blood examinations in the fifteen years of observation is recorded in Table I. It will be noted that the lowest blood values were observed on Feb. 3, 1927, when the hemoglobin was 6 Gm. per 100 c.c. and red blood cells 2,072,000 per cubic millimeter. During this admission also, the depth of icterus was most marked. Since 1933 the hemoglobin and red blood cell count have shown little fluctuation. The blood smear (Fig. 4) was typical of Mediterranean anemia and revealed nucleated red cells, moderate polychromatophilia, poikilocytosis, hypochromic microcytes and macrocytes, stippled cells, and occasional target cells. Pale, thin, and leaflike macrocytes, containing irregularly clumped hemoglobin with intervening areas possessing staining defects, were also noted. The icteric index was frequently elevated, the highest reading being 23. The span of fragility in this patient extended from 0.4 per cent saline to 0.25 per cent, although intact cells were still noted in the 0.175 per cent dilution. In the control test, hemolysis began in 0.425 saline and was complete in the tube with the 0.325 per cent solution.

TABLE I

BLOOD STUDIES OF D. M.

DATE	AGE (YR.)	HEMOGLOBIN (GM.)	R.B.C. (MILLION)	W.B.C.	HEMATOCRIT (%)	RETICULOCYTES (%)	TRANSFUSION (C.C.)
11/27/26	4	8.5	3.70	9,600		11.0	300
2/ 3/27		6.0	2.07	8,600		2.0	300
4/22/29		7.0	2.76	8,600			250
5/16/31		9.7	2.87	5,600			
9/ 7/33	11	9.6	3.88	11,050			
2/11/35		10.0	3.50	9,600			
3/ 6/39		9.0	3.50	5,600	30	6.5	
3/25/40		9.0	3.80	6,200	30		
4/ 6/41	18¾	8.0	3.75	13,360	34	4.5	

Following the first admission, the spleen gradually increased in size and by July, 1927, extended to the level of the umbilicus. The liver edge was palpable from the start but never increased in size. The intensity of the cardiac murmur has varied in different periods from barely discernible to loud, with such wide transmission as to suggest rheumatic heart disease. The heart has also shown corresponding variations in size.

The last hospital admission was on April 20, 1929, and three days later he received 250 c.c. of blood. Following discharge, the patient was observed periodically in the outpatient department of the Beekman Hospital. No further transfusions have been given. When last examined on April 6, 1941, the patient weighed 130 pounds and his height was 70.5 inches, the latter measurement being considerably above the average for his age. His facies (Fig. 1) bears a striking resemblance to reported patients of comparable age with the same disease.[1, 2, 3] The gaunt features, long facies, slight slant to the eyes, prominent cheek bones, peculiar pallor, and slight icterus of the skin and sclerae contributed to this appearance. His heart was not enlarged, the apex was in the fifth space at the nipple line, and the systolic murmur was soft and less intense than in childhood. The liver was 2 cm. and the spleen 9 cm. below the costal margin and extended to the level of the umbilicus. Despite these physical findings and the state of chronic anemia, the boy has done very well in school, he has participated in physical activities without undue fatigue, and infections of the upper respiratory tract have been infrequent.

In the early period of observation the patient was thought to have von Jaksch's anemia. It was only as erythroblastic anemia gained wider recognition that appropriate roentgenographic studies were made. The skeletal changes together with the physical and hematologic features presented by this patient clearly indicated that the anemia belonged in the category described by Cooley. The first x-rays in 1931 and those repeatedly made in subsequent years revealed similar findings.

Fig. 1.—Patient D. M. at 18 years of age.

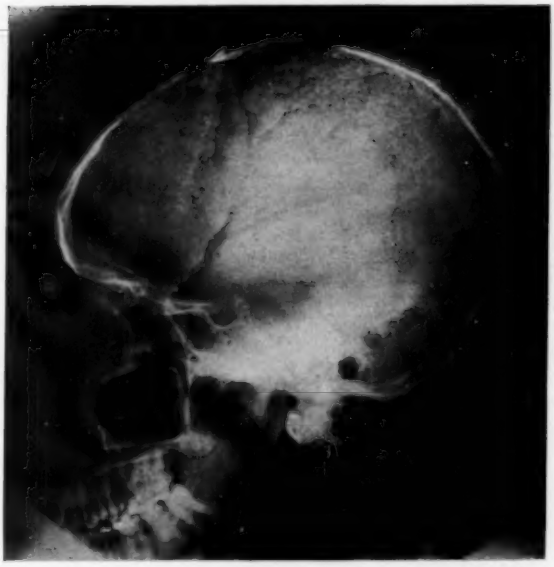


Fig. 2.—Roentgenogram of the skull of patient D. M. Note widened diploic space, thinning and atrophy of the outer table, osteoporosis, and granular appearance.

Lateral views of the skull (Fig. 2) showed a widened diploic space which was mottled and osteoporotic. The outer table was atrophied and could not be visualized in the parietal and occipital areas. Vertical striations were not present. Trabecular atrophy with subsequent coarse reticulation and striation due to regeneration of new bone was most apparent in the bones about the elbow (Fig. 3*A*) and involved principally the proximal portion of the ulna and the distal portion of the humerus. There were no changes in the metacarpals, metatarsals, or other small bones.

Members of D. M.'s Family

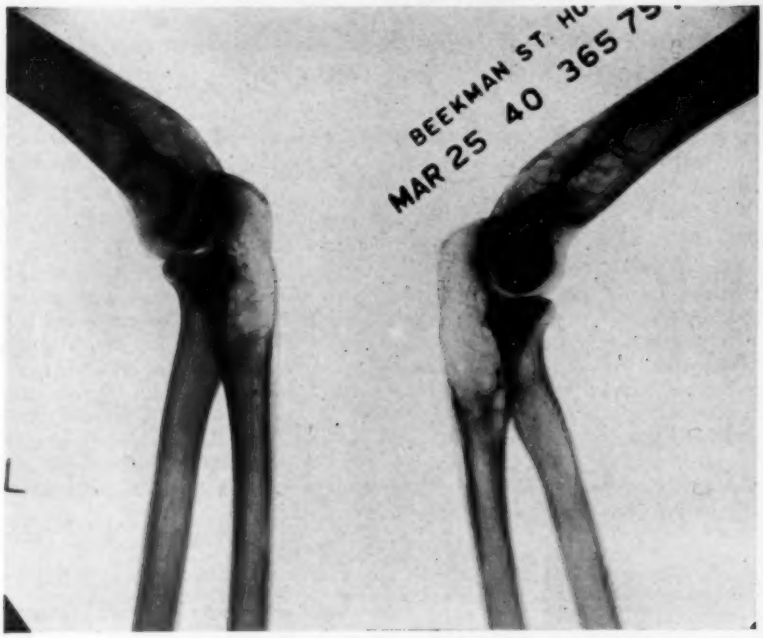
Remaining Children.—Seb. M., a brother, was born on October 31, 1924, and has always been in excellent health. Physical examination showed a very well developed boy of 17 years with normal features, in whom neither the spleen nor liver was enlarged. Blood examination (Table II) revealed, however, a slight lowering of the hemoglobin, red blood cell count of over 6 million cells per cubic millimeter, stippled cells and target cells, slight polychromatophilia, hypochromic macrocytes, and increased resistance of the red blood cells to hypotonic saline solutions. *X*-ray examination showed a normal skull and the only skeletal change was observed in the right elbow (Fig. 3*B*). This was most noticeable in the ulna and consisted of a trabeculated zone of osteoporosis 5 cm. from the proximal end of this bone.

TABLE II

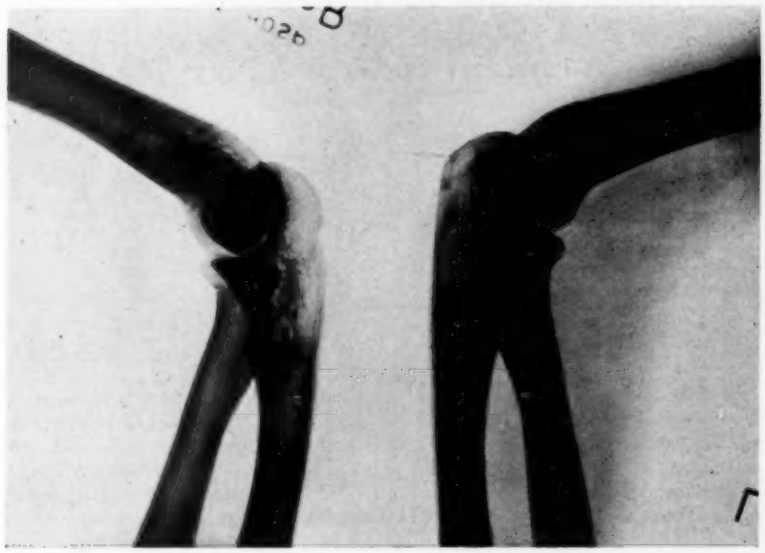
BLOOD STUDIES IN THE FAMILY OF D. M.

	FATHER (P. M.)	MOTHER (D. M.)	PATIENT (D. M.)	BROTHER (SEB. M.)	PATIENT (S. M.)
Age (Yr.)	53	44	19	17	8
Hemoglobin, Gm./100 c.c. blood	12	13	8	11.8	9
R.B.C., millions/cubic millimeter	4.31	5.26	3.75	6.13	3.36
Volume of packed R.B.C./100 c.c. blood	43	44	34	43	30
Mean R.B.C. volume, cubic microns	99	83	90	70	89
Icteric index	15	4	23	–	6
Stippling, average number of cells/100 oil immersion fields	2.1	1.8	1.8	3.1	2.3
Target cells	+	0	+	0	+
Anisocytosis	+	+	+++	+	+++
Poikilocytosis	+	0	+++	0	+++
Hypochromia	+	0	+++	+	+++
Polychromatophilia	+	+	++	+	++
Macrocytes	+	+	++	+	++
Nucleated R.B.C./100 W.B.C.	0	0	8	0	8
Fragility test					
Hemolysis begins	0.4	0.425	0.4	0.375	0.425
Hemolysis ends	0.25	0.325	0.25	0.25	0.225

Sam M. was born on July 1, 1933. A hemoglobin of 60 per cent was noted at 6 months of age and again at 9 months, when the red blood cells numbered 5,320,000 and the white cells 27,000 per cubic millimeter respectively, with a normal predominance of lymphocytes. This leucocytosis is not uncommon in the early stages of Mediterranean anemia. A systolic murmur was first heard at 18 months, a palpable spleen at 2 years, 9 months, and the initial roentgenographic changes consisting of osteoporosis of the skull appeared at 3½ years. These changes have progressed so that now at 8 years of age this boy presents the hematologic, roentgenographic, and physical characteristics of a classical case of Mediterranean anemia of moderate severity. The blood examination recorded in Table II represents one of many similar studies. In addition to the anemia, the blood smear



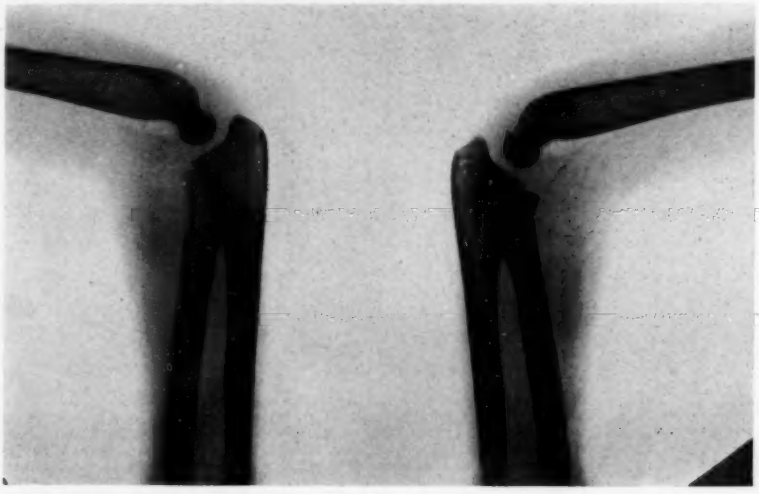
3A.



3B.

Fig. 3.—Roentgenograms of the elbows of *A*, patient D. M. and his brothers, *B*, Seb. M., and *C*, Sam M. Note rarefaction, osteoporosis, coarse reticulation, and trabeculation. In the patients D. M. and Sam M. involvement is chiefly in the distal end of the humerus and of the proximal portion of the ulna of both sides. In the carrier Seb. M. the most marked change is in the proximal end of the right ulna.

shows moderate anisocytosis, poikilocytosis, polychromatophilia, stippling, normoblasts, target cells, and some unusually large hypochromic erythrocytes. The fragility test shows extreme resistance of the erythrocytes to dilute saline solutions. The plasma has at times been moderately pigmented and the last icteric index on June 14, 1941, was 18. Roentgenograms reveal evidence of cortical thinning and medullary widening in many of the skeletal structures. Osteoporosis and thickening were observed in the skull, in the ribs, and in the metacarpals which were widened and squared. The bones about the elbows showed the decalcification and trabeculation noted also in his other brothers (Fig. 3*C*). The heart was enlarged,



3*C*.

and a loud systolic murmur was transmitted to the axilla. The liver measured 4 cm. and the spleen 7 cm. below the costal margin. The mongoloid features, prominent malar bones, protruding upper lip, and muddy yellow complexion were more pronounced in this boy than in his older brother at a comparable age. This patient was never transfused and his management was similar to that of D. M. His blood has in recent years maintained a level which has fluctuated within narrow limits. As in his brother, this state of chronic anemia has not resulted in either physical incapacity nor in increased susceptibility to infections.

Parents.—P. M., the father, is 53 years old and was born in Sicily. His features are normal. He has always engaged in hard physical work. Examination revealed no abnormalities. His liver and spleen were not palpable. In April, 1930, he contracted syphilis and was vigorously treated until 1932. Since November, 1930, all serologic and spinal fluid tests have been negative.

As noted in Table II, the icteric index is slightly elevated. The hemoglobin is slightly lowered and the blood smear (Fig. 5) reveals slight anisocytosis, poikilocytosis, polychromatophilia, a moderate number of hypochromic macrocytes, stippling, and a few target cells. The red blood cells showed increased resistance to hypotonic saline solutions. Roentgenograms of the skull and other skeletal structures reveal no abnormalities.

D. M., the mother, 44 years old, was born in Sicily. She has always been active and physical examination revealed no abnormalities. The spleen and liver were

not palpable. Her facies was normal and neither she nor her husband bore any resemblance to their affected sons, D. M. or Sam M. In 1930 her Wassermann was negative. In March, 1931, following the diagnosis of syphilis in her husband, her Wassermann was found to be positive. She received active treatment and this was continued during her pregnancy until May, 1933, just before the birth of her last child, the patient Sam M. Numerous Wassermann tests have been negative since February, 1932. Repeated spinal fluid tests have also been negative.

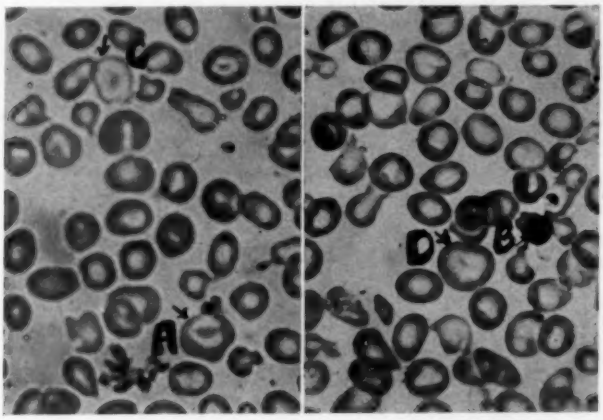


Fig. 4.—Blood smear of patient D. M. *A*, macrocyte presenting target appearance, characterized by concentric dark and light zones; *B*, normoblast; *C*, thin, pale, leaflike red cell containing small central clump of hemoglobin surrounded by unstained area; *D*, macrocyte with large central achromic area. This erythrocyte was found in increased numbers in this patient and in Sam M. and to a lesser extent in the remaining members of the family. Note poikilocytosis, anisocytosis, and hypochromia.

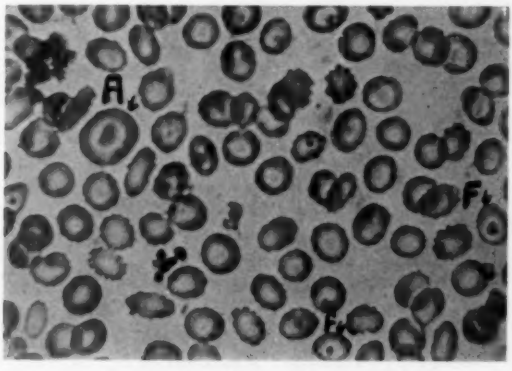


Fig. 5.—Blood smear of the father, P. M.: *A*, macrocytic target cell; *F*, smaller target cells. Note poikilocytosis, anisocytosis, and hypochromia.

Blood examinations show no anemia. The peripheral smear, however, reveals a small number of hypochromic macrocytes, slight polychromatophilia, and stippled cells. The fragility test is within the normal range. Roentgenograms of the skull and other bones were always normal.

COMMENT

The patients described in this report include two individuals from the same family, one 8 years of age, the other 19 years of age, both affected with Mediterranean anemia of moderate severity. The latter, who was observed from the age of 4 years, still possesses as a young adult the characteristic hematologic, roentgenologic, and physical features of this blood disorder. Early in the course of the illness this patient received three transfusions, the last in 1929. The spleen was not removed and antianemic therapy, such as liver, iron, and copper, were administered without affecting the blood level. Now at 19 years of age, in spite of chronic anemia, this boy is tall, well developed, and participates in all activities without handicap. On the basis of the favorable experience with this patient, his younger brother has been treated symptomatically and he has never been transfused.

Increasing numbers of cases of the milder type of Mediterranean anemia occurring in adolescents and in young adults have recently been reported. These are summarized in the paper by Wintrobe and coworkers[2] who include an additional case of their own in a young man of 18 years. In this paper are described abnormalities of the blood in this youth's family and in two other families. Other cases falling into the same category are a brother and sister of 17 and 20 years, reported by Atkinson,[1] and the case of a young man of 20 years reported by Dameshek.[3]

The case presented in this paper demonstrates that in addition to the classical cases of Mediterranean anemia which are already severe in early infancy and which do not reach puberty, there is a milder group for whom a longer life expectancy may be predicted. In these instances the disease usually does not become manifest until later childhood. The patient D. M. shows that even cases of moderate severity in childhood may without splenectomy ultimately pursue a benign course. The disease in the 8-year-old brother appears to be following a similar pattern. Additional confirmation of the existence of a mild type of Mediterranean anemia is afforded by its unsuspected presence in apparently healthy siblings and in parents. While the milder cases escape clinical recognition until later childhood, examination of the blood in early infancy may reveal incipient changes. This was observed in the case of Sam M., the younger brother, whose blood in the first year revealed evidences of anemia and increased numbers of white cells although splenomegaly and skeletal changes did not appear until the third and fourth years, respectively.

Among the members of the milder group, differences in degree of anemia exist, and it is doubtful whether the same hopeful prognosis for prolonged survival can be held out for the entire group. The correlation between different degrees of severity of Mediterranean anemia and life expectancy will be determined only by more extensive experience.

The parents of these patients, born in Sicily, and their one remaining unaffected child, a son of 17 years born in this country, appeared to be normal and healthy and in none was the spleen palpable. Roentgenographic examination showed no skeletal changes nor was the granular skull indicative of osteoporosis so frequently noted in arrested cases present in either parent. The skull of the normal boy of 17 years also showed no changes. In the right elbow, however, a zone of trabeculation and of osteoporosis was noted which was marked in the proximal portion of the ulna. This was bilaterally present in his affected brothers. In the 17-year-old boy described by Atkinson,[1] a similar abnormality was also discovered.

Examination of the blood revealed well-defined abnormalities in the parents and in their healthy son. In the smears of all three, varying numbers of hypochromic macrocytes and of red cells with basophilic stippling were observed. In the father and brother, the red cells also showed increased resistance to hemolysis in hypotonic saline solutions. In them the hemoglobin was only slightly reduced, but the red cells showed abnormalities in size and shape, and many of them revealed a thinness characteristic of this disease. The brother's blood showed a decreased hemoglobin, but the cells numbered over 6 million per cubic millimeter. Erythrocytosis has been described by Wintrobe and co-workers[2] in similar cases and is regarded as a compensatory mechanism for cells of reduced volume and hemoglobin content.

These blood alterations in apparently healthy members of a family in which one or more were affected with Mediterranean anemia are of paramount importance. They point to the fact that the disease may be latent and that this so-called tendency may be detected by careful blood studies. The individuals possessing these blood changes have been designated as carriers of this disease and they represent the source of inheritance. The presence of hematologic abnormalities in every member of this family suggests that the trait is inherited as a dominant, a view also held by Cooley.[4a] Increased resistance of the red cells to hypotonic saline solutions was observed in both parents in the case reported by Atkinson[1] and in several of the cases in the series recorded by Caminopetros.[5] The latter investigator was the first to emphasize the importance of the fragility test as a means of detecting carriers of this disease. In other families, however, blood changes occur in only one parent. The prolonged resistance span of the erythrocytes serves, therefore, as a useful means of segregating these individuals.

In addition the variations in shape and size of the red cells, the presence of hypochromic macrocytes, of target cells, and of stippled cells constitute important elements in the detection of carriers. The observations of Wintrobe and his co-workers,[2] showing that the red cells may undergo morphologic changes with little or no anemia, is significant. Of diagnostic importance also was his emphasis on the frequent finding of

red cells with basophilic stippling. In the family under discussion, hypochromic and polychromatophilic macrocytes and stippled cells represented the most common abnormalities encountered, regardless of the severity of the disease.

While stippled red cells were found in every member of the family, the number of these cells never exceeded 3 per 100 oil immersion fields. In each instance at least 200 fields were carefully inspected. It has been claimed[6] that a small number of red blood cells in normal individuals may show punctate basophilia. Undoubtedly the numbers of these cells will vary with the type of stain, differences in technique, and in the number of fields examined. In my experience in staining by Wright's method stippled red cells have rarely been observed in the blood of normal children. When found in more than occasional numbers, investigation usually revealed other evidences of increased bone marrow activity.

In a previous communication[7] three types of macrocytes were described in Mediterranean anemia. These were target cells, hypochromic macrocytes, and large, pale, leaflike erythrocytes containing irregularly distributed and clumped hemoglobin with surrounding areas that take little stain. The last type, the most characteristic of this disease, appears to be excessively thin, an impression that is heightened by the ridges and wrinkling frequently observed within its structure. In two cases of this disease, Bradford and Dye[8] noted macrocytosis and thinning of the red cells following splenectomy. Thinness may constitute a fundamental defect in morphogenesis of the erythrocytes in Mediterranean anemia. If thin, flat cells are sufficiently numerous, they may account for the increased resistance to hemolysis in dilute saline solutions in contradistinction to the ease of hemolysis of the spherical cells in hemolytic jaundice. Further studies are required to test this hypothesis in Mediterranean anemia.

Macrocytic cells should be sought for in the milder type of Mediterranean anemia, for in established cases, particularly after splenectomy, the blood smear is characterized by macrocytosis, some of the cells reaching sizes of unusual proportion. Blood smears filled with abnormally large, thin red cells produce a unique hematologic picture. Large, acromic macrocytes appear, however, when the anemia is moderate or marked, and for this reason they were frequently noted only in the blood of the two patients, D. M. (Fig. 4) and Sam M. Target cells appeared also in their blood and in that of the father, but they were not observed in the smears of the mother or of Seb. M. Target cells were originally described by Barrett[9] and were subsequently observed in the blood of infants and children with Mediterranean anemia.[7] These cells cannot, however, be regarded as specific, since they may be observed in a variety of anemic conditions. In a recent communication, Cooley[4b] also stated that target cells do not bear a specific relation to Mediter-

ranean anemia and that a wide resistance span does not depend upon their presence. The target appearance in macrocytes (Figs. 4 and 5), however, is more suggestive of Mediterranean anemia. On the other hand, hypochromic macrocytes, target and nontarget in appearance, were observed in the blood smears of every member of the family. In the adult patient reported by Eliel and Bayles,[10] the microcytic smear was punctuated by smaller numbers of hypochromic macrocytes. Judging from the mean red cell volume, the blood of Seb. M. showed a microcytosis, while the blood cells of his parents and brothers were normal or slightly increased in volume. The blood of Seb. M. illustrates the type of Mediterranean anemia with microcytosis and polycythemia. While numerous macrocytes characterize the blood of advanced cases and are greatly multiplied following splenectomy, in the milder group they may be few in number. Macrocytes are not mentioned in all cases, and in the family reported by Strauss, Daland, and Fox[11] the blood picture was one of uniform microcytosis.

There is no single cell that may be regarded as specific for Mediterranean anemia. The hematologic diagnosis of the mild forms of this disease depends, therefore, upon the presence of a variety of abnormal cells, and one or more of these should be looked for in the smears of these and of early cases.

Consanguineous marriage, regarded as common in families with Mediterranean anemia,[4b] did not occur in the present case. It is also unlikely that syphilis in the parents which was contracted ten years before and which was successfully treated at that time produced any lasting effects upon their blood picture. Mediterranean anemia in their youngest son, following their infection and treatment, differed in no wise from the anemia in their firstborn. The mild anemia in the apparently unaffected son born prior to their infection corresponded to the carrier type of anemia in the parents. Moore[12] and others[13, 14] pointed out that secondary anemia occurring with syphilis may be expected to respond to routine antisyphilitic treatment.

While Mediterranean anemia is frequently referred to as erythroblastic anemia, the unsuitability of the latter term is apparent from the absence of nucleated red cells from the peripheral blood of the carriers and from that of the milder clinical cases. Normoblasts were found in the blood of D. M. and Sam M. but in none of the others. Many of the reported cases of the milder type also have failed to reveal normoblasts. The occurrence of unquestionable Mediterranean anemia in two individuals in one family and of disturbed erythropoiesis in the others lends weight to the hypothesis that these blood disorders represent variations of a single disease. The carriers may be regarded as persons with the mild type of anemia that ordinarily escape detection. The term "carrier" is employed in a limited genetic sense to describe the asymptomatic case in whom blood and roentgenographic changes, how-

ever minimal, are present. This individual is fully equivalent, genetically speaking, to his sick sibling so that the children of both run the same risk of inheriting Mediterranean anemia in any of its clinical forms.

In a number of recent reports, anemias of a familial nature among Italian and Greek patients have been described. Reference has already been made to the studies of Caminopetros[5] who detected the disease in several generations, principally by the wide resistance span of their red cells. Confirmation of these observations has been made in the families reported by Atkinson,[1] Wintrobe, Matthews, Pollack, and Dobyns,[2] and by Dameshek,[3] and probably by the Italian family of Strauss, Daland, and Fox.[11] The Italian patient described by Eliel and Bayles,[10] who at 39 years of age had a severe refractory anemia and splenomegaly dating from childhood, may also be included in this category. These results confirm Caffey's original hypothesis,[15] that mild cases of Mediterranean anemia may reach adult life and constitute the source of transmission of the disease.

The familial aspects of the case here presented suggest that this disease is more prevalent in Italian and perhaps Greek populations than is generally considered. It is possible that there are individuals with mild forms of this disease who have perhaps been suffering with an unexplained and low-grade chronic anemia. The disease may be latent in healthy individuals, it may be mild and remain undetected, or, as in the present case, it may become arrested after a period of acute anemia. In the light of available studies, Mediterranean anemia should be considered in the differential diagnosis of an obscure anemia in a young child of Mediterranean parentage before roentgenographic changes are observed or before the spleen becomes enlarged, when it is found to be refractory to antianemic therapy. The familial aspects of Mediterranean anemia which were exemplified by the case described in this paper are not unique and have been observed in ten other families to be reported in a subsequent communication.

SUMMARY

In two generations of a family consisting of five individuals, there were two patients with typical Mediterranean anemia, while the blood of the remainder revealed distinctive red cell abnormalities.

One of the patients was a youth now 19 years of age who has been under observation since 4 years of age. Transfusions were required to combat the anemia in childhood. He still presents the classical, clinical, hematologic, and roentgenographic evidence of Mediterranean anemia. In spite of chronic anemia he has without splenectomy or other recent treatment developed normally, participates in all activities, and has shown no undue susceptibility to infection. He exemplifies the type of patient with Mediterranean anemia of moderate severity who is asymptomatic until after infancy and who reaches adult life after the blood

dyscrasia has become arrested at a level compatible with well-being. This case adds to the increasing evidence that Mediterranean anemia may exist in other forms than that of the better-known severe and rapidly progressive type in which there is a fatal outcome before puberty.

A younger brother, now 8 years of age, also has Mediterranean anemia comparable in severity with that of his older brother. The remaining members of the family include the parents and a son, 17 years of age. They appear to be clinically well and in none is the spleen palpable. Roentgenographic changes are absent in the parents, but in the son a zone of trabeculation and osteoporosis is present in the proximal portion of one ulna, a lesion which is also present in both affected brothers. Despite minimal anemia, the blood in each member of the family showed various abnormalities, and of these basophilic stippling and hypochromic macrocytes were the most common features. With the exception of the mother, the red cells of every member of this family were resistant to hemolysis in hypotonic saline solutions.

The blood abnormalities in the three apparently healthy individuals characterize them as carriers of this disease. The carrier may be detected by examination of the blood smear, by the fragility test, and by skeletal changes. Basophilic stippling, hypochromic macrocytes, and increased resistance of the red cells to hemolysis constitute important hematologic features and may be present with little or no anemia.

It was pointed out in the text that the term carrier is employed in a limited genetic sense to describe the asymptomatic case. Available evidence indicates that the inheritance of this disease is direct from parent to child and the chances of transmitting it are alike in the asymptomatic as in the well-established case.

The occurrence of typical Mediterranean anemia in two individuals in one family and of anemia of varying degrees in the others lends weight to the hypothesis that these blood disorders represent manifestations of a single disease.

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BLOOD PRESSURE OBSERVATION ON CHILDREN IN PRIVATE PRACTICE

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OUR study comprises 4,492 blood pressure determinations on 1,469 young people from 3 to 19 years of age.

The readings were carried out by two members of our office staff. In cases suggesting the unusual, the findings were rechecked by each individual. In order to eliminate emotion, the readings took place at the completion of the study, and if fright or antagonism was evident, the test was repeated after a suitable rest period.

Patients with acute illness or temperature elevation were not included. The number of determinations in excess of the number of patients was accounted for by repetition in certain individuals at different ages.

For demonstration purposes, our findings are presented in four age groups; the majority in each group is so outstanding that it is looked upon as representing the normal variation for that age period (Table I).

TABLE I

	NO.	NORMAL	HIGH	LOW	SYSTOLIC	DIASTOLIC
Group 1	193	144			80-100	50-70
3 to 6 yr.			27		100-130	70-90
				22	50- 80	30-50
Group 2	406	287			80-100	50-70
6 to 9 yr.			107		100-130	70-90
				12	70- 80	30-50
Group 3	358	254			90-110	60-80
9 to 12 yr.			54		110-140	70-95
				50	80- 90	50-60
Group 4	512	344			110-120	60-90
12 to 19 yr.			65		120-150	80-90
				103	70-100	40-60
Total	1,469	1,029	253	187		

Factors Influencing Blood Pressure in Children
Familial. May be elevated or low as a family characteristic
Emotion. Incident to determination procedure
Adolescence
Kidney disease
Thyroid gland disorders

It has been claimed by careful clinicians that elevated blood pressure may precede demonstrable kidney disease by several months. In our cases, blood pressure was found elevated only when a diseased kidney was proved.

Presented before the Academy of Medicine Fortnightly, Oct. 23, 1941.

It is reasonable to suppose that the thyroid gland with its manifold functions in the young could be subject to disorders of a temporary as well as a persistent nature.

Hypertension in association with tachycardia, tremor, tantrums, and other evidences of nerve imbalance is not infrequently found dependent upon a so-called *hyperthyroidism*.

In like manner *hypothyroidism* often will be made apparent by hypotension associated with a minus basal metabolic rate and brachycardia.

Either habitually high or low blood pressure in the child strongly suggests the necessity for a study relating to thyroid gland function.

Essential hypertension of undetermined origin is of rare occurrence in children. Comparitively few cases have been reported in medical literature. For those interested, this subject is ably presented by Goldblatt et al.* and by Sobel.†

An analysis of 253 cases with elevated blood pressure reveals the following:

163 Classified as Neurosis, Representing Nonpathogenic Deviations From the Normal State of the Nervous System
- Male 105
- Female 58

66 Clinically Proved Hyperthyroidism
- Male 21
- Female 45

17 Kidney Disease
- Male 10
- Female 7

4 Cardiac
- Male 2
- Female 2

3 Pulmonary Tuberculosis
- Male 1
- Female 2

In 187 the blood pressure was persistently subnormal.

97 varying types of malnutrition, anorexia, loss in weight, absence of gain in weight and statural growth were the outstanding complaints. There was one case of anorexia nervosa (Simmond's disease) in a girl 14 years of age.

90 were proved hypothyroid, including cretins and other forms of thyroid gland deficiencies.

This group was proved hypothyroid by response to the therapeutic test of desiccated thyroid therapy.

Of 1,469 cases 1,029 group themselves with the normal blood pressure for age.

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*Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: J. Exper. Med. 59: 347, 1934.

†Sobel, I. P.: Am. J. Dis. Child. 61: 280, 1941.

TABLE II

REPRESENTATIVE TYPES OF BLOOD PRESSURE ABERRANCIES

	AGE	NUMBER OF READINGS	SYSTOLIC (AV.)	DIASTOLIC (AV.)
Neurosis:				
B. S., female, mentally and physically normal; reaction to procedure	3	3	130	80
Familial:				
D. F., male; strong, vigorous boy in excellent health; highest B.P. reading 150/100; father's B.P. habitually over 200	12-14 15-17 17-19	16	118 120 130	70 72 80
Adolescence:				
W. S., male; normal healthy boy; highest B.P. reading, 140/80	12-14 15-17	14	126 129	74 80
Hyperthyroid:				
J. S., female; highest B.P. reading, 144/78	9-10	8	135	75
Hypothyroid:				
R. S., male; excellent health; readings taken during administration of 2 gr. of desiccated thyroid daily, lowest B.P. reading, 92/55	18-19	17	110	66
Nephritis:				
M. H., male; acute hemorrhagic nephritis; urine characteristic; highest B.P. reading, 150/94	12-14	3	150	90

Our study emphasizes that every child after the third year should have a complete physical examination at least every six months, which is not complete without a careful blood pressure determination.

In carrying on the above study, we are greatly indebted to two members of our office staff, Miss Emma Godfrey and Miss Alice Kelly.

American Academy of Pediatrics

Proceedings

ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS.—OCT. 9, 1941

Panel Discussion on Diagnosis of Obscure Intracranial Conditions of Childhood

Chairman: Eric Oldberg, M.D., Ph.D., Professor and Head of the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago, Ill.

Associates: Percival Bailey, Ph.D., M.D., Professor of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago, Ill.

Paul C. Buey, M.D., Associate Professor of Neurology and Neurological Surgery, University of Illinois, College of Medicine, Chicago, Ill.

Bronson Crothers, M.D., Assistant Professor of Pediatrics, Harvard Medical School; Head of the Neurological Service, Children's Hospital, Boston, Mass.

Gilbert Horrax, M.D., Neurosurgeon, Lahey Clinic, Boston, Mass.

Franc Douglas Ingraham, M.D., Instructor in Surgery, Harvard Medical School, Visiting Surgeon, Neurosurgery, the Children's Hospital, Consultant in Neurosurgery, Boston Floating Hospital, Associate in Surgery, Peter Bent Brigham Hospital, Boston, Mass.

Differential Diagnosis of Pontine Tumors

Percival Bailey, Ph.D., M.D., Chicago

After a long experience over a period of several years in a clinic we have seen a great many brain tumors. I did not learn a great deal about such tumors as they affected children because the clinic dealt largely with adults. The hospital had no children's service other than listed connection with a children's hospital.

When I began a pathologic study of the material which came into that clinic, I set aside from the other brain tumors the cases which affected the pons because I was interested in trying to find some means by which one could make a prognosis of the pathologic phenomena of that type of tumor. When I went to Chicago in 1928 and received from the three pediatric hospitals, the University of Chicago, the Children's Memorial, and the Milwaukee Children's, I found I could not argue about

tumors of the brain as they affected children in the same way as I could those affecting adults. I found difficulty in handling tumors of the pons in children. I was not alone in this; I found as the material accumulated that the tumors were almost always misdiagnosed by the pediatrician and also by the consulting neurologist. The diagnosis made almost invariably was encephalitis or poliomyelitis or some other form of infectious disease. I tried to find the characteristics whereby they might be recognized and also what conditions would have to be differentiated in connection with them. In the course of the last ten or fifteen years, I have accumulated perhaps twenty-five or twenty-six such cases. I shall tell you briefly about three of them that illustrate fairly well their characteristics.

The first was a girl 3 years old. She had been well until she fell on her head, after which her mother noticed that she squinted. She seemed to have been stunned by the blow, although she did not perhaps become unconscious. She became rather sleepy and listless, did not play as she used to, was apt to stumble when she walked, and her mother noticed after a while that she dragged her right leg.

When she was brought to the hospital for examination, she was lethargic, without any apparent desire to play, and did not want to get out of bed; she had a paralysis of the third nerve on the right side, and the pupils were enlarged. We were unable to make a satisfactory sensory examination because she did not cooperate, but there seemed to be no loss of sensitivity to pain anywhere over the body. She had no leucocytosis although she ran a fever. Her temperature was above normal but sometimes was below 98° F. She had the Babinski sign on both the right and left sides, but it was decidedly weak on the right side and inclined to be spastic. We did a lumbar puncture and found twelve cells in the spinal fluid, all of them apparently lymphocytes.

The case was diagnosed as encephalitis, and the child was discharged from the service. She was taken to another hospital and was examined again; another lumbar puncture was done and twenty lymphocytes were found in the spinal fluid. A diagnosis was made of hemiplegia alternans though the consulting neurologist suspected the child might have a tumor without objective evidence. The child declined rapidly and died; autopsy revealed a soft tumor involving the left cerebral cortex.

The second case was a boy 4½ years old who had been previously well. When he was brought to the hospital, his mother stated that three weeks before he had had a very severe sore throat. He recovered from the sore throat in a few days but afterward was unsteady on his feet, did not want to get out of bed, squinted, lost his appetite, and often vomited. When this had gone on for three weeks, it was seen that he liked to lie quietly in bed, making little effort to sit up or occupy himself. He had a facial paralysis of a peripheral type on the left side. He could look upward and downward and to the right, but he could not turn his eyes to the left. If placed on his feet, he was very unsteady, staggered, and fell over backward. His extremities were flaccid, but he had a Babinski sign. There was no obvious loss of sensitivity to pain. He had an irregular fever. The fundi were normal. When tapped on the head, there was no indication that the sutures were separated. A lumbar puncture was done and he was found to have fifteen lymphocytes in the spinal fluid.

A diagnosis was made of polioencephalitis. This was made by the pediatrician and by the consulting neurologist. They agreed he had some sort of polioencephalitis. His condition progressed. He developed difficulty in swallowing and a chronic ulcer on the right side, and it was found he had an involvement of the fifth and seventh nerves on the right side. After four months he had pneumonia and died.

At autopsy it was found he had a tumor of the pons; the pons was swollen, and he had what was formerly called a hypertrophic tumor of the pons.

The third case was a female child 7 years of age. She had been well previously. The doctor who was called found her ill with a fever and weakness of the right leg. He decided she had poliomyelitis (it was at a time when cases of poliomyelitis were being recorded) and sent her to the Municipal Contagious Hospital. There she was examined; a lumbar puncture was done and the spinal fluid was found normal. It was then learned that she had been unsteady on her feet for three or four months previously. In walking she usually leaned against a fence. She also complained of double vision and had not done well in her school work. She also had occasional vomiting.

The physician at the Municipal Contagious Hospital made a diagnosis of brain tumor and transferred her to my service. On examination, her fundi were normal; x-ray of the head was normal. She was listless, ataxic when she tried to walk, and would fall over to the left. She had a sensory loss in the fifth nerve distribution on the left side, a loss of pain sense on the right side, and she had weakness of the sixth and seventh nerves on the right side.

At that time I had become sensitized to these cases so that a diagnosis of a tumor of the pons was made. The child was given x-ray treatment. She improved considerably almost immediately and was able to go home. The effect of the x-ray therapy was quite transitory and after fifteen months she died, when the typical swelling tumor of the pons was found.

These cases occur not infrequently. Heretofore, apparently they have gone undiagnosed and will continue to go undiagnosed for some time in the future. They constitute 15 or 20 per cent of intracranial tumors in children; the problem is one of considerable magnitude in the field of children's neurology.

To make a general summary of the symptomatology of these cases, we may say that this condition occurs in children between the ages of 3 and 14 years, the peak being around 11 or 12 years. Unusually the children begin to vomit as one of the earliest symptoms without complaining of headache or without having any defect in vision. It is not accompanied by other signs of increased intracranial pressure. They have signs of cerebellar involvement and disturbance in walking, and they are apt to fall over backward when placed on their feet. They are less apt to have the usual peripheral signs that we find in adults. All the extremities are flaccid even though they have a positive Babinski sign and ankle clonus. The sensory changes are slight. It is difficult often to make a good sensory examination. Usually the sensory findings are slight except those due to involvement of the fifth nerve. Almost always they have an irregular fever, which may rise to a considerable height. It is not accompanied by other symptoms such as a leucocytosis.

These children are apt to have vascular hypertension. In several cases the blood pressure is unusually high. When a puncture is made an increased number of lymphocytes in the spinal fluid is found. The lymphocytosis is due to the pressure of the tumor on the meninges. Any tumor in the neighborhood of the vascular cistern may give rise to an increase in the number of leucocytes in the spinal fluid. Quite a number of these cases show an increase in the number of these cells in the spinal fluid.

These tumors are almost always gliomas; there is infiltration and they spread around the nerve fibers and cells so that they reach a considerable size before they destroy many nerve cells, when, for that reason, the symptoms develop. The tumors arise within the pons and spread into the cerebellum or into the cerebral peduncles. They may spread so as to fill up the vascular cistern.

Some of them are malignant, and some, not so malignant, cause trouble because of the situation they occupy.

An interesting thing is that although they lie near the cerebral aqueduct they rarely shut off this structure. The enlargement of the pons seems to occur without

involvement of the aqueduct, so that they do not produce a disturbance of the circulation of the spinal fluid. Therefore they lack the evidences of increased intracranial pressure which accompany intracranial tumors in general. The physician is misled by many things. The cardinal symptoms of intracranial tumor are vomiting, headache, and swelling of the opticonasion, and any one of these may not be present.

Vomiting in children occurs from many causes. No pediatrician is likely to think of a brain tumor merely because a child vomits. Nevertheless, if a child continues to vomit, whether he complains of headache or disturbance of vision, the possibility of intracranial tumor is likely to occur to the physician or the consulting neurologist. He should not be misled by the absence of signs of increased intracranial pressure or by the history.

The symptoms suggest a fall or blow on the head, so that some sort of hemorrhagic intracranial condition is suspected. Again these symptoms following a sore throat lead one to suspect an infection. What misleads the neurologist are the multiple palsies of the cranial nerves. When a neurologist is confronted with no symptoms of increased intracranial pressure and a lot of palsies, he begins to run over in his mind those things that may cause palsies of the cranial nerves. He thinks of polioencephalitis, hemorrhagic encephalitis superior, or poliomyelitis anterior. He thinks about acute multiple sclerosis and about polioencephalitis or Heine-Medin disease.

When he does that he forgets the one thing I spoke about in the beginning, and that is that you cannot think about children the same way you think about adults. All those conditions are diseases of adults. Poliomyelitis anterior is a pathologic curiosity which continues to be handed down in the textbooks and never has been found by the neurologist. Multiple sclerosis is a disease of adults and does not affect children, and they are not apt to have Heine-Medin disease.

When such a diagnosis has been made, in my experience the condition has always turned out to be a tumor of the pons. When a child develops multiple palsies of the bulbar nerves, one can be quite certain that a pontine glioma is present. A real differentiation has to be made between tumors of the fourth ventricle and other tumors in the neighborhood. Symptoms and signs from tumors in the fourth ventricle are usually intermittent in character and are usually accompanied by periods of increased intracranial pressure.

Tumors of the pineal body give rise early to increased intracranial pressure. Usually there is not much difficulty in making the differentiation. The only differentiation that is practically impossible to make is that of a solitary tubercle in the pons. Solitary tubercle in the pons used to be a rather common disease, if you believe the older textbooks. Nowadays one rarely sees a solitary tubercle of any form in the brain. The only ones I have seen in ten or fifteen years have been a couple in Mexican children and one or two in negro children who have come from the South. One case diagnosed as glioma of the pons turned out to be such a tubercle. All the other cases that have come under my observation in the last ten years have been diffuse gliomas of the pons.

CHAIRMAN OLDBERG.—What this boils down to is that whenever one has a case develop insidiously, involving cranial nerves, he ought to have his fingers crossed before he makes a diagnosis of encephalitis at the start. Then if it progresses quite fast and takes in more cranial nerves as time goes along, he ought to make sure he is dealing with a case of encephalitis and not with a tumor of the pons?

DR. BAILEY.—That is correct. The symptoms of palsy may develop rather acutely.

CHAIRMAN OLDBERG.—As far as treatment is concerned, it is almost invariably x-ray treatment?

DR. BAILEY.—That is right. However, I should add one thing. Occasionally when a diagnosis of pontine tumor is made, if the intracranial pressure rises very high, I think in rare cases it is permissible to explore surgically. I made such a diagnosis once and refused to operate. When someone else operated on that patient and the whole posterior portion of the pons cerebelli was found to be packed with material which was cleaned out, the patient made a good recovery.

CHAIRMAN OLDBERG.—Was that a child?

DR. BAILEY.—Yes. He also had increased intracranial pressure so that it was different from the majority of the cases of pontine glioma. While occasionally pontine gliomas that give rise to increased intracranial pressure are seen, the majority of cases have no increased pressure, so there will be a striking difference in those two groups. I have already had some half dozen of these cases come under my care, but I was not fortunate enough to find one for whom anything could be accomplished.

Cerebral Palsy

Bronson Crothers, M.D., Boston

This symposium theoretically is on the diagnosis of obscure intracranial conditions. Some of these, I should think, are almost artificially so.

The situation presented is that of a child who is inadequate on account of a cerebral injury. Ordinarily the diagnosis is very simple and complete. On the other hand, the textbooks have confused or oversimplified it. Since the management of the child with cerebral injury is very largely a study in subtraction and the surgeon has made it even more so than the orthopedist, it seems very important that we start off with an appraisal of what has been done.

If you assume that the studies of the actual pathologic changes are too elaborate to neglect, and if you assume that cerebral injury is not an active lesion, you are neglecting the controversy as to whether the lesion is congenital or prenatal or postnatal. One should start off with an appraisal of the anatomic depth of the lesion. What is really useful is the physiologic and psychologic residue.

The difficulty with all these children is that at the beginning they have a situation that can be defined only in motor terms. A little baby with an inadequacy of motor control is a relatively simple physiologic problem. At that point there is no particular difficulty. You decide whether the baby is athetotic and whether the destruction is so great that nothing can be done.

It is interesting that the textbooks call cerebral palsy spastic paralysis. It is perfectly obvious that even a severe injury of the brachium pontis at birth may produce no spasticity for a long time. As to the relation of the actual spasticity to the severity of the lesion, there is absolutely no way that I know of appraising the structural causes in terms of stiffness and spasticity alone. It seems essential to realize that spastic paralysis is a good sign of the degree of cerebral injury. These children can be sorted out gradually, but one must be cautious the first year or two. Later the situation begins to bring in intellectual factors so that they must be appraised also. By that time the characteristic features of the group as a whole is extreme irregularity. Many of these children talk well and talk sense and yet later cannot get on in school.

Since the lesion itself is invariably extremely diffuse, the child has all sorts of sensory and motor difficulties which are not to be determined by the sense of touch or recognition of heat, cold, and so on. There are difficulties in the recognition of form and things of that sort. The ordinary psychologic appraisal has to be regarded with a good deal of skepticism and reserve since it may be inadequate to recognize the real difficulty.

As a child gets along to 4, 5, or 6 years of age, usually the question comes up as to whether orthopedic apparatus is useful, and there the orthopedic consultant often betrays both the patient and the physician who sends the patient to him, because almost without exception he seeks to get balance by subtraction. He subtracts often from a shifting capital and often from an increasing capital. It takes a long observation before you know enough to appraise the capital from which subtractions can be safely made. Aside from the mutilating operations, there are all sorts of apparatus which abolish rather than increase the activity of special joints and muscles.

These children are put through muscle training procedures. Often they are extremely time-consuming and of an expensive type, and they are checked up almost indefinitely. I happen to be one of the chief offenders, because for many years we have encouraged people to return at short intervals for procedures that improved the child or at least were coincident with improvement of the child. We know that a child grows up anyway and that none of the cases is stationary. The only way to control this very difficult situation is to watch with intense interest the surgical attack on these very features in a large enough group of cases. There is always the possibility that someone can find a procedure that includes the finding of progressive lesions in what seems to be a fixed situation. The question as to whether you perform an operation depends on what you can accomplish without operation.

If the pediatrician is patient, kind, and optimistic, he can take better care of the child up to 12 years of age. During this time the child responds to conservative treatment and sometimes does surprisingly well. Then comes a period between 12 and 18 years when life suddenly becomes very difficult. Following the protection throughout early childhood, he reaches adolescence, and in the ordinary accepted meaning of that term, attempts to break away from restraints. This develops into a psychiatric situation which is often appalling.

I have taken care of all sorts of children with neurologic diseases and know the pessimistic side of the cases. I know that every single child who has a permanent difficulty will have problems. The only ones of these children who have tried to commit suicide have been the aggressive relatively intelligent cerebral cases between 15 and 20 years of age. There is absolutely nothing that one can do for them at 18 years unless he can change their pattern. As they are, life to them is actually not worth living. The children who go through the serious type of cerebral palsy are those with unusual charm and social background that have made them impregnable to those pressures that have killed the other children.

Since most of the therapy is either very long-continued or is subtractive and mutilating in nature, we ought to be able to so phrase our diagnosis that medically, at least, it will be translated accurately into educational and social aspects by those who are responsible for the child. It requires accurate psychologic appraisal and it requires considerable observation. It requires above all a knowledge of neurology.

The control of emotion is associated with profound changes in intellectual capacity and great irregularity of growth and development. The changes from adolescent to adult are partly dependent upon the responsibility of the individual and his development and partly on how much sense he has. Unless this is recognized, you will go through the distressing situation of bringing up a child under highly protected influence, then having to withdraw the protection, have no place for him to go.

CHAIRMAN OLDBERG.—In listening to your sympathetic talk, it seems to me you have pointed out several phases that perhaps I can go over in my own language.

These children suffer from a deficit as far as the nervous system is concerned. The nervous system being a part of the structure of the body that does not regenerate, these children are missing something which can never be replaced. In some parts of

the nervous system this results in subtracting from certain functions and in some parts this results in hyperstimulating certain functions.

There is a particularly pronounced relationship between the physical deficit and the psychologic problem, particularly when the child reaches adolescence. We can reduce that to a simple demonstration which everyone has seen. When one enters a ward in which some of these cerebral-palsied children are, such a simple thing as suddenly clapping the hands will send the child into a tremendous amount of hyperkinesis. If this is true and if worry over appearances to outsiders will double and treble the disability, as it does, of course, when the added stress of adolescence and increase in intelligence comes, the psychologic problem involved is tremendous. It is in this as well as in the medical field that the pediatrician must lend his very best efforts and his best human sympathy.

DR. CROTHERS.—There is another element also. There is a large number of people with cerebral-palsied children in their families, who survey the opportunities for cerebral-palsied children in the way of special schools, workshops, and other opportunities. These children can be taken out of competition. It is a fascinating problem to work out.

A physician who is taking care of these children ought to be a realist. People will blame you if you are too optimistic, and yet if you do not offer the children any training you are at fault. My feeling is that there has been too much uninformed optimism, which results in pressures, disappointments, and frustrations.

I should rather make an effort to be right in my prognosis even though I am a pessimist, and I happen to be a pessimist on this question. That is why this noble assemblage of neurosurgeons has my sympathy when it tries to correct a neurologic picture which seems to me so distressing.

DR. BAILEY.—I understood Dr. Crothers to say that one should begin by making a neurologic appraisal, although he intimated that it was not important unless one were going to do something about it mechanically. I would like to question him about that.

Even on necropsy, when the brain is in your hand, it is exceedingly difficult to find any relationship between the neurologic appraisal and the physiologic deficit. I do not know why it is necessary to start a neurologic appraisal. Why should one not make a physiologic appraisal, and then, if it seems possible to do something mechanically or surgically, make a neurologic appraisal?

There is a tendency on the pediatric service to want to do an encephalogram immediately. Even though the child is an imbecile and cannot feed himself, you get an encephalogram.

DR. CROTHERS.—A great many of these children ought not to be treated. I am sure of that. If you can say with certainty that from the physiologic picture and the psychologic appraisal you know all there is to know, the encephalogram is futile. My feeling is that you use encephalography when you can get results and can find something that was not suspected before. Another indication is when parents feel that every possible opportunity must be exhausted by the physician who advises them that the child has no future alternative whatsoever. If they feel that this is the final thing before giving up, that is a perfectly good indication for taking the risk.

We are using encephalography less than we did. I should do it if I had the slightest doubt in the presence of an active lesion. The ordinary x-rays and the lumbar punctures do not give much, if any, information. Young children with hemiplegias have shown enough pathology by the method to make us adopt it as a rule.

Whether young babies should have this procedure done is a question to be considered, since there is a possibility that something may be found that was not suspected.

One thing that gives me confidence in encephalography is that in the presence of a growing structure the effects of these injuries at different ages are apt to be forgotten. If you have some idea of the effect of these devastating injuries upon the structural growth of the bone and can relate it to the psychologic appraisal of the children, I would be the first to say that encephalograms should be made.

DR. BAILEY.—I was not objecting to encephalography. My question was only one of procedure. I understood Dr. Crothers to say that one should begin by making an anatomic appraisal.

DR. CROTHERS.—By anatomic I mean the process of getting back to a localization by looking at the physiologic appraisal and relating that to the anatomic situation, and then deciding. An anatomic appraisal means looking at the brain.

What I am pleading for is to get the medical procedures into such an intelligent pattern that you can translate them easily, fairly, and accurately, and tell the parents what they have to do with the child who is damaged in this particular way. I think that gap is great at the present time. "Spastic paralysis" means nothing to teachers or parents.

Surgical Treatment of Chorea Athetosis

Paul C. Bucy, M.D., Chicago

Dr. Crothers presented to you rather pessimistic attitudes and outlooks on the neurologic problems of children. With my persistent optimism, I shall try to tell you about the things we have tried to do with some of these children, although I would like to stress that the particular phase of the problems of cerebral palsies is a small one, and I might agree with Dr. Crothers that the outlook for many of these children, severely damaged both mentally and physically, is pessimistic, and one cannot have a very hopeful outlook because so much cerebral tissue has been damaged that it cannot possibly be replaced.

Athetosis is a part of this picture and not only ourselves but physicians for many, many years have been familiar with the condition of athetosis. We have seen these children with twisting and turning involuntary movements of their extremities and have wished we could do something about it, and we did not know what we could do.

Furthermore, we did not know much about the nervous mechanism which gave rise to these involuntary movements. We have taken the brains out of these children who have died and have examined them and, as Dr. Bailey said a moment ago, although we held the brains in our hand, we had a very limited conception of the mechanism responsible for the troubles of these children.

Our neuropathologists and neurologists as well finally concluded that in a majority of instances the lesion lay somewhere in the basal ganglia. Often it is in the motor cortex of the pyramidal tract and in some cases in the anterior column of the spinal cord. That did not mean very much to us in terms of physiology, and nothing in terms of treating the child. Those structures were destroyed, and it was obvious that what was not there could not possibly be giving rise to those movements. Therefore we concluded that the destruction of the basal ganglia must release some other structure in the nervous system to cause the hyperactivity that induced these involuntary movements. We did not know how it released it, and we did not know what was released. That was partly due to our own unwillingness to look at what few facts we had.

Early in the present century the late Sir Victor Horsley demonstrated in at least three cases that if he removed the cerebral cortex anterior to the rolandic fissure, what many of us have known as the motor cortex or the precentral cortex, it would abolish the involuntary movements of athetosis. That was almost entirely ignored by the neurologists, the neuropathologists, and everybody else, with one exception.

The late Kinear Wilson had observed that if people who suffered from these involuntary movements developed a hemiplegia on that side, the involuntary movements stopped after the hemiplegia. He therefore concluded that the nervous structure which was released by destruction of the basal ganglia or the motor cortex of the pyramidal tract which descends into the spinal cord caused certain impulses to be transmitted to the sigmoidal muscle. He was alone, a voice crying in the wilderness, and nobody paid much attention to that observation.

In 1931 Dr. Buchanan confirmed Sir Victor Horsley's observation. Subsequently we concluded that Kinear Wilson was right in general, but it appeared that rather than the pyramidal tract it was other fibers descending from the motor cortex by a more circuitous route.

Then came the physiologic observations which finally clarified the entire picture. They demonstrated that from certain small parts of the cerebral cortex there were certain suppressor nerve impulses which, when activated, would suppress the activity of the motor cortex, that these suppressor impulses were transmitted not to the rest of the motor cortex but to the cortex nuclei and to the rest of the basal ganglia and back again to the motor cortex.

It is obvious why a lesion in the motor cortex gives rise to these involuntary movements, because it destroys the suppressor inhibitory or controlling influence which comes from the stripped areas on the rim of the motor cortex. When that suppressor effect is abolished, hyperactivity at the rim of the motor cortex results.

Obviously we can do nothing about this suppressor influence which is destroyed. We cannot replace it. We can only hope to help these people and to abolish their involuntary movements by interfering with or subtracting the neuro-organism which gives rise to these involuntary movements.

We know from our observations that these movements can be stopped by removing the precentral cortex, and also from the observations that this impulse travels down, not in the pyramidal tract, but primarily through the anterior column of the spinal cord. These movements can be definitely ameliorated by sectioning the anterior column of the spinal cord.

We know nothing at the present time as to the exact course of the impulse from the motor cortex to the anterior column of the spinal cord. We know that these known pyramidal fibers transfer to the different parts of the brain. Some go to the basal ganglia, some go to the midbrain, and some go to the pons. From there they are relayed to the spinal cord. Exactly which ones of these are concerned with the involuntary movements we do not know.

At the present time any operation directed to interrupting these impulses in the subcortical areas of the brain must be regarded as purely experimental in nature. We do not know enough at present to advocate a subcortical procedure for the relief of these movements.

Therefore, the surgical procedures open to us in the case of involuntary movements are of two kinds. We can either operate on the cortex of the brain or we can operate on the spinal cord. Each of these procedures has its advantages. They are not applicable to the same type of procedure. Operating on the anterior columns of the spinal cord is effective but not completely so. Although the movements are diminished in activity, they are often not abolished. In a fair percentage of cases, and the exact percentage is not at present known, the initial improvement which is achieved with this operative procedure is not permanently made. In the course of

one or two or three years, the movements increase in intensity, although they do not usually return to their initial violence. Therefore, there is a definite limitation on this operative procedure, although I would not imply to you that the operation is not without benefit. Even though the movements are not completely abolished, the diminution in intensity is gratefully received by the patient.

The operation has two very definite advantages. Operating on the anterior column of the spinal cord, if successfully done, is not associated with any paralysis or any increase in the paralysis which may exist prior to operation. That is a very definite advantage, and for that reason operation is applicable to the bilateral cases; that is, those individuals, of whom there are many, who have involuntary movements of both sides of the body. They can have a bilateral operation and receive improvement, whatever it may be, on both sides.

The operation on the cerebral cortex is one in which I have been most interested as to its limitations and applicabilities, which are quite different. The removal of the precentral cortex, naturally, is associated with the development of considerable paralysis. That must not and cannot be overlooked. In those cases in which paralysis already exists, it is often increased. Sometimes it is too great to be increased. In those cases in which little or no paralysis exists prior to operation, a variable degree of paralysis, usually with some spasticity, develops after operation.

The amount of paralysis that develops following the removal of the motor cortex varies from case to case. Although I do not have sufficient cases from which to draw a final conclusion, I am inclined to think that it varies with the age and that the older the person and the greater the paralysis, the greater the deficit which will result from the operative procedure. In the younger person the deficit is not so great. That remains to be conclusively demonstrated.

The paralysis which results from this is not a complete one, as we had supposed a few years ago. All of these people recover sufficient voluntary control in the muscles of their lower extremities to enable them to walk quite well. Many of them enjoy walks of several miles. The deficit which occurs in the upper extremity is far greater than in the lower extremity. I have seen none in which the upper extremity has been completely paralyzed. It always can be moved, and in those cases where it was useful before operation, some degree of usefulness is usually maintained, although it is not great.

On the credit side of the ledger, all of these people have abolition of their involuntary movements immediately after operation. In our early cases we were very cautious as to the amount and the exact location of the cerebral cortex which we removed, and in those cases the complete abolition of the involuntary movements has not been maintained. They have had a return of a small amount of their involuntary movements, particularly in their fingertips. In no case has the return been great. In all cases there has been a striking reduction in the violence and intensity of their involuntary movements. Later as we extended the extirpation and have included all of the precentral cortex to the rolandic fissure and have increased the extent of our extirpation up and down the precentral gyrus, the improvement and permanency of it has been definitely increased. Many of our cases now are doing very much better than our earlier cases did, and I am convinced that a general extirpation in this region brings the most permanent and satisfactory results.

In deciding which of these cases is suitable for this operative technique, there are certain definite things which we must take into consideration. The removal of the precentral or motor cortex is not applicable to the bilateral cases. It cannot be carried out successfully on the bilateral cases because these movements return after removal of the motor cortex, particularly to the legs, and, to a lesser extent, to the arms. Therefore, if you remove both of the cortices you will completely paralyze the individual. There is no question but that the procedure is not adaptable to

bilateral cases. It is limited to those cases where the involuntary movements are exclusively unilateral or very predominantly unilateral. I have occasionally operated upon patients who had a slight movement on one side and a varying movement on the other side. Those cases have not done so well as the cases in which the movements were exclusively unilateral. In those people who have a certain degree of usefulness of the extremity in spite of their athetosis, you, as well as the patient and the patient's family, must carefully balance what you are going to subtract against what you are going to give them. You are going to produce a certain degree of hemiplegia. Make no mistake about that. You are going to take away his involuntary movements. Are the involuntary movements sufficiently severe to warrant leaving the patient with a hemiplegia? That is the question which you and the patient must decide.

CHAIRMAN OLDBERG.—What you have been talking about is not a panacea at all, but something to be applied to cases in which there is really not much to be lost, no matter what you do. That applies to the operation of cutting the extrapyramidal tracts in the cervical spinal cord or to your strip tease operation on the brain. In either case I would then be a little more emphatic than you were about the advisability of choosing only the unilateral cases.

Even in the spinal cord operation, if one has to divide the extrapyramidal tracts on both sides of the spinal cord and, particularly, if he decides to do that in one stage, he is likely to produce an immediate respiratory paralysis. Of course, he takes a slight risk if he does an operation like that in two stages. Such an operation should be restricted to unilateral cases. In either case I think we should regard this discussion this morning as a hifalutin private discussion rather than as something that ought to be publicized to the rank and file as being a panacea. It is still in the experimental stage.

DR. BUCY.—I agree entirely with what Dr. Oldberg has to say. I should call your attention to the fact that my experience has been almost exclusively with the cerebral operation. My experience with the spinal cord operation has been unfortunate. When I speak of the operation on the anterior column of the spinal cord, I am forced to speak from my knowledge of the experience of others. Dr. Oldberg has had some experience with it and I am sure we should pay close attention to the limitations which he feels necessary to place upon that procedure.

I agree entirely with Dr. Oldberg as to the experimental nature of this procedure. As I indicated to you, my own earlier experiences with it were not so satisfactory as those at the present time, and I still feel there is a great deal to be learned, from a physiologic standpoint, from cases of this type.

The number of cases to which it is applicable is small. Certainly it is not what we desire as the optimum type of procedure. No one in his right mind wants to give someone a hemiplegia in order to relieve something else. At the present time with our present knowledge that is the only way I know of to relieve those persons permanently.

CHAIRMAN OLDBERG.—I agree.

DR. CROTHERS.—I would like to know how many of these individuals of the strictly hemiplegic type are young persons. I would like to know whether the pattern changes in such cases as they grow up. We have seen children with athetosis appearing at 1 year of age who have shown considerable improvement later. I have not seen it disappear.

The other question is that of cooperation with the patient in what may be a long-term mutilating physiologic experiment, and whether you have done it so far on children whose own judgment is particularly good.

DR. BUCY.—We have not operated on many young children. The majority with which I have had experience have not been birth injuries, congenital lesions, or anything relating to birth.

One young man who was operated upon when he was 26 years old is quite alert and intelligent, and his cooperation is excellent. His disability dated from birth, but the majority of the disabilities developed as a result of trauma, acute infectious disease, or something of that nature, considerably later than birth.

DR. BAILEY.—There is another phenomenon which is important, and that is spasticity. I would like to ask Dr. Bucy whether he has had any experience in attempting to relieve spasticity.

DR. BUCY.—The procedure does not benefit spasticity but invariably makes it worse or, if there was no spasticity previously, it produces some. There was some reason to hope that the operation on the anterior column of the spinal cord might relieve spasticity. I have tried it. It does not.

Pineal Tumors of Childhood

Gilbert Horrax, M.D., Boston

Before starting to tell you something about these rather obscure tumors, let me try for a moment to refresh your minds about the pineal body and some of the theories in regard to it and what we believe to be its present function, if any.

The pineal body is a small structure that lies just above the quadrigemina at the posterior end of the third ventricle. For many years there has been speculation as to whether it had any function or not, and whether it was a gland or not. It has been the subject of a great deal of controversy and experimentation. All of the experiments which have been made are conflicting. There is evidence in some forms of life of the histologic structure of the body, but there has been no definite evidence in man, except in the embryonic stage, that the pineal body is glandular. It is a body which is part of the brain structure and which contains certain cells like small lymphocytes.

Tumors involving the pineal body had been found in children before the period of puberty, and in some of those children there were very striking characteristics of a constitutional nature, particularly an increase in the early development of sexual function when they were 5 to 10 years of age. They became sexually potent, they had pubertal hair, axillary hair, and their voices changed. With the finding of a pineal tumor occasionally, there resulted a belief that it was a glandular body. The difficulty is that certain other tumors are associated with this same type of early sexual development, namely, tumors of the third ventricle, and it is well known that tumors elsewhere, such as ovarian tumors, may be associated with this curious syndrome of pubertas praecox. Only a small percentage of the tumors of the pineal body in children show this syndrome. At the present time, we cannot say that the pineal body has a glandular structure.

Pineal tumors represent a relatively small percentage of any tumor series. I have personal knowledge of about twenty-five of these tumors in persons of all ages. There were fourteen to fifteen in Dr. Cushing's series at the Peter Bent Brigham Hospital. At the Lahey Clinic, we have had eleven more cases. In the Brigham Hospital series there were five in the prepubertal age, and in my series there have been five. Two of the Brigham Hospital patients had this striking syndrome. One of my five cases has shown a very striking picture. Out of the ten cases in children, only three have shown the true Pellizzi syndrome. Pineal tumors, both in

adults and children, do not represent over 2 per cent of all the tumors of the brain. You can see that only a small proportion of the pineal tumors have the pineal syndrome.

The symptomatology of pineal tumors may be divided into three categories. First are the subjective symptoms. Dr. Bailey spoke about tumors of the midbrain, which began with symptoms of pressure on the cranial nerves, palsies, and hemiplegia. Tumors in the region of the pineal body press down upon the cranial nerves and produce pressure symptoms immediately. Only later do symptoms of headache, choked discs, and sometimes unsteadiness occur which are the early symptoms of the pineal tumor, as would be the early symptoms of any kind of brain tumor which caused an increase in cranial pressure.

Another symptom of which we have seen several instances is polyuria. Why these patients should have polyuria I do not know. In some cases that have come to autopsy we have found there was an extension of the pineal growth, an implantation through the third ventricle to the region of the pituitary structures and probably involvement of the mechanism which has to do with water balance and, therefore, the polyuria.

The second category of symptoms are the neurologic signs. First are the choked discs and the pupillary changes. These children have dilated pupils which do not react to light. The size of the pupils may change from time to time.

A second feature is that a tumor in this situation produces absolute loss of conjugate movement of the eyeballs upward. They can look to the side and downward, but there is absolute inability to look above the horizontal plane. That has been very characteristic.

The third feature is the retroversion. That is more or less true of any tumor that lies along the midline of the cerebrospinal axis. It is particularly true of those in the pineal body. The patients have a tendency to fall backward when placed in the Romberg position. There are cerebellar cycles. Sometimes these tumors extend down to the cerebral fossae. The choked discs and the retroversion are some of the most characteristic symptoms.

The third category of symptoms includes those which are in the metabolic sphere. It is a very striking picture when you see a child 4 to 7 years old, who has adult genitals, who has axillary and pubic hair, whose voice has changed, and who has all the muscular development of an adult physically and sometimes mentally.

One must make a diagnosis first and often that can be made definitely when you have the combination of symptoms which I have just been over. But the neurosurgeon wants more than that. We know from experience that a symptom complex which is typical of a tumor in a certain area may not always be true. Many cerebellar tumors may produce a lot of these changes. A ventriculogram shows a definite shadow bulging into the posterior region of the third ventricle. That is a differentiation between a tumor in this region and one in the cerebellum, though sometimes cerebellar tumors may push forward.

For many years pineal tumors were thought to be inoperable. Then we began to operate just for the relief of pressure symptoms, because we knew we could not get at them. We have also operated upon some pineal tumors and have been able to extirpate them. It is a dangerous operation. You are dealing with a structure between the hemispheres which is difficult to get at and can be reached satisfactorily only by a spreading operation between the occipital lobes, or sometimes by going through a ventricle, if the ventricle is wide enough. In the larger ones or the more diffuse ones the only way is by taking off part of the hemisphere in the occipital lobe so that you can reveal what you have to deal with. That is a serious operation. The mortality is high.

Some of these pineal tumors are helped very definitely by x-ray therapy for a long period of time. I have some evidence for that.

There are two kinds of tumors, the pinealomas and the duramatomas. If you have a duramatoma there is only one attack and that is radical surgical attack. The duramatoma would not be affected by x-ray. If you have a patient with a pinealoma, almost always there is increased pressure and a decompression must be done, followed by x-ray treatment.

When they have choked discs, I have been doing merely decompression and x-ray treatment. Of the eleven cases, we have four who have done very well over periods from four months to two years with this type of treatment, which is less hazardous than the radical extirpation. X-ray has a definite role for therapy.

Of the eleven cases at the Lahey Clinic, upon three radical extirpations have been attempted. Two are alive and well. One of these is a stenographer who has been able to do her work perfectly well for four or five years. One was a boy who had an outspoken symptom of pubertas praecox, but he failed after operation and lived only two months. The third is still alive after eight years and is in fairly good condition but with a recurrence of her tumor. She has had another series of x-ray treatments.

(Demonstration of Slides.)

In summary, pineal tumors in children are as rare as they are in adults. The treatment should be decompression and x-ray and, if that fails, a radical attack upon the tumor.

CHAIRMAN OLDBERG.—May I ask what is the sex distribution of tumors arising from these cells?

DR. HORRAX.—Of the eleven cases from the Lahey Clinic, there were five females and six males. It is very curious that although pineal tumors occur in children of both sexes, the syndrome of pubertas praecox has never been demonstrated in girls.

CHAIRMAN OLDBERG.—Whenever pubertas praecox occurs in a boy, if there are the pupillary and ocular movement findings, one can make a diagnosis of a tumor involving the pineal body.

I have seen female children with symptoms of pubertas praecox who had suprasellar cysts and did not have pineal tumor.

It would be a good thing to point out that this aberration in the early condition of puberty seems to be confined to boys as far as pineal tumors are concerned.

DR. BAILEY.—Even in boys the association of intracranial tumor with pubertas praecox would not make a diagnosis of pineal tumor. Involvements of various sorts have been associated with the syndrome of pubertas praecox. I would like to ask Dr. Horrax if he has seen similar cases.

DR. HORRAX.—Yes, I have.

DR. BAILEY.—You also said that naturally one would not try to treat a duramatoma by x-ray. How can you make a differential diagnosis clinically between a duramatoma and a pinealoma?

DR. HORRAX.—I have seen only one duramatoma where there were teeth or possibly bone.

DR. BUCY.—How is decompression going to be of much value in these individuals with an obstruction in the third ventricle? Have you had the experience

where a decompression of the third ventricle was associated with x-ray therapy, and where x-ray therapy was beneficial in relieving the obstruction and in decreasing the size of the tumor?

DR. HORRAX.—I have had no experience with ventriculostomy. Although I have realized that is theoretically unsound, it has always seemed to me that even a part of a decompression in the presence of a tumor of this kind did relieve pressure. If you do a decompression and subject the child to x-ray treatment, the tumor will be affected definitely and will often subside. I think ventriculostomy would be possible but perhaps a little more difficult.

CHAIRMAN OLDBERG.—The fact is that tumors such as you describe, while rare, make up 2 per cent of intracranial tumors, and are worth while diagnosing both from the standpoint of therapy and from the standpoint of extraordinary interest.

Subdural Hematoma in Infancy

Franc Douglas Ingraham, M.D., Boston, M.D.

For several years in the Children's Hospital, we have been very much interested in subdural hematomas in infants, and we have been trying to determine the actual incidence.

For the present purpose we will limit the age group to the first two years of life, since the hematomas after that age are more like those found in adults.

It seemed obvious that this could be considered an obscure condition and that diagnosis had to be made by mechanical measures. It seemed that we had to be more articulate in differentiating the type and number of these cases without hematoma before discovering their relative incidence. It was of interest to find that the positive results were increased as greater efforts were made to clarify the diagnosis.

The most striking feature has been variability of symptoms and signs. I would like to show photographs of a number of infants with hematomas, mostly before anything had been done to them, to show the great variation in appearance.

(Demonstration of Slides.)

It has been clear that these patients, more commonly than not, seemed to be very ill. Frequently they seemed to be fairly well with only minimal signs and had almost exactly the same pathology. We have, therefore, resorted to tapping, and have not had any difficulty with that procedure. We feel that one should go quite far away from the midline and through the suture line rather than through the fontanel. In that way we can make the diagnosis definitely. The spinal fluid has been negative in more than half of these patients and is, therefore, of very little help.

I have not separated the patients who had subarachnoid as well as subdural bleeding. I have attempted to separate the former patients from those who had a clot in the subdural stage, as was demonstrated in the seventy-one operations.

DR. HORRAX.—Just how do you go about deciding whether you should turn down the bone flap on these children or whether you use some other method of surgical treatment?

DR. INGRAHAM.—I did not mean to go into the treatment of these infants. Usually we have turned down the bone flap on all the patients with an actual membrane because we feel the membrane should be removed in order to give optimal

opportunity for development in the brain. That is different from the currently accepted treatment of hematoma in adults. They do very well with simple drainage in a good many cases.

We have had only one patient who was known to have had a clot before the clot was removed. He had a very striking atrophy and went downhill in the course of that year. Because of the rapid growth of the brain in this age period, we feel it is important to remove these membranes when one would not think it necessary with adults.

DR. BAILEY.—Dr. Ingraham is right in including those over 2 years of age with the adult cases. In my experience there is a definite difference between those cases which occurred immediately after birth and those which occurred in the first year of life.

DR. INGRAHAM.—There has been very little difference if there was an actual membrane present. If there was diffuse bleeding, they behaved differently. There are fewer of those cases that proved to have membranes. They are not included in this group. They may have extensive hemorrhage and not have a membrane or a solid clot demonstrated. When they have such I think they behave very much like the patients who are older.

DR. BUCY.—One point worthy of being stressed, and I am sure it is what you intended, is that although the tapping through the fontanel is a useful diagnostic procedure and may be useful in diagnosing a sick child, it is only rarely a curative procedure. It is a mistake to tap these patients in the hope of curing the condition, because damage will be done to the brain.

DR. INGRAHAM.—I will agree that in most of these babies a Verhoef operation should be done, and if one can evacuate part that way, that is the final step.

DR. CROTHERS.—It is important to recognize that the puncture itself is a serious diagnostic procedure. A competent member of the staff should direct the punctures. The puncture should be part of the surgical attack rather than an isolated diagnostic procedure.

QUESTION.—What are the physical signs of birth injuries? Should treatment consist of (1) nothing, (2) lumbar puncture, or (3) decompression?

DR. CROTHERS.—If a baby appears to be physically intact but is not doing well, steps must be taken in connection with some organized plan.

QUESTION.—Why are these cases of subdural hematoma generally bilateral? Is irrigation enough in those immediately following birth?

DR. INGRAHAM.—I do not know why they are bilateral. The irrigation will certainly get rid of the partially clotted blood but will not affect the membrane, and we feel it is important for the membrane to be removed.

QUESTION.—Kindly give the diagnostic methods of subdural hematoma and the technique of subdural tap.

DR. INGRAHAM.—It is very difficult to make the diagnosis without the taps, and we would hope that the presence of a clot might be suspected in any sick infant who had not some other obvious diagnosis, since we had minimal signs with some of these patients.

The technique of the tap is relatively simple. We sterilize the scalp. We use a needle that is about No. 20 gauge with a short bevel, and hold the point of the needle in the fingers of the left hand so it will not go in too easily, putting a little back pressure on it, and press gently against the suture line. It is possible to feel the dura and stop immediately after the dura is penetrated.

QUESTION.—Chronic adhesive arachnoiditis will give symptoms which are difficult to differentiate from intracranial tumors. May we have some discussion on this subject?

DR. INGRAHAM.—In most instances the difficulties in diagnosis are so great that it is not accomplished. In the majority of instances the diagnosis of adhesive arachnoiditis is a surgical advance. Occasionally you may suspect an adhesive arachnoiditis in a child with hydrocephalus, but it is unusual to make a positive diagnosis prior to operation.

QUESTION.—Regarding pontine tumors, is there any distinctive quality about vomiting or vomitus, projectile vomiting, etc., or any blood in gastric content or stools, as has been described in other cerebral tumors?

DR. BAILEY.—There is nothing characteristic about the vomiting and it is difficult to learn from the younger children whether they are nauseated or not. There is never any blood in the vomitus, so far as my experience goes. Occasionally patients have a gastric hemorrhage associated with pontine tumors.

QUESTION.—Is a clot likely to be formed before the age of 6 months as well as later?

DR. INGRAHAM.—With the membrane present, they act like those that occur later. The height of our age incidence was in the first few months of life. Taking all the cases up to two years, there were more in the first four months than later.

QUESTION.—What about the term pachymeningitis hemorrhagica or is this out?

CHAIRMAN OLDBERG.—The term "pachymeningitis hemorrhagica" is a term which is rather dangerous to use, because it is a condition that Verhoeff described as associated with subdural hematoma. Verhoeff thought it was a disease. It occurs in adults and not in children. Verhoeff thought it was associated with people who drank alcohol or people who had epileptic symptoms, syphilis, and so on. Actually, these conditions cause people to fall down and bump their heads often. I think it is a dangerous connotation although scientifically it is a correct term.

If we make a diagnosis of pachymeningitis hemorrhagica and do not do something about it, we may miss a subdural hematoma and have a dead patient.

News and Notes

CHILD HEALTH DAY—1942

BY THE PRESIDENT OF THE UNITED STATES OF AMERICA
A PROCLAMATION

WHEREAS the Congress by joint resolution of May 18, 1928 (45 Stat. 617), has authorized and requested the President of the United States to issue annually a proclamation setting apart May 1 as Child Health Day:

NOW, THEREFORE, I, FRANKLIN D. ROOSEVELT, President of the United States of America, in recognition of the vital importance of the health of children to the strength of the Nation, do hereby designate the first day of May of this year as Child Health Day.

And I call upon the people in each of our communities to contribute to the conservation of child health and the reduction of illness among children by exerting every effort to the end that before May Day, Child Health Day, children over nine months of age be immunized against diphtheria and smallpox, the two diseases for which we have the surest means of prevention.

IN WITNESS WHEREOF I have hereunto set my hand and caused the seal of the United States of America to be affixed.

DONE at the City of Washington this sixth day of February in the year of our Lord nineteen hundred and forty-two and of the Independence of the United States of America the one hundred and sixty-sixth.

(SEAL) FRANKLIN D. ROOSEVELT

By the President:

CORDELL HULL

Secretary of State.

Dr. A. Ashley Weech, Associate Professor of Pediatrics at Columbia University, College of Physicians and Surgeons, has been appointed B. K. Rachford Professor of Pediatrics at the University of Cincinnati Medical College to become effective July 1. He will be Chief of Staff and Medical Director of the Children's Hospital and Director of the Children's Hospital Research Foundation.

Prof. Heinrich Finkelstein died January 28, 1942, at Santiago, Chile, of typhoid fever complicated by a cardiac condition. He was 76 years of age. Professor Finkelstein was a distinguished teacher of pediatrics and in former years his classes in Berlin were attended by many American pediatricians. He was an honorary member of the American Pediatric Society.

In a letter from Katherine N. Lenroot, Chief of the Children's Bureau, to state health officers, the importance of an immunization program, due to the likelihood of epidemics resulting from the shifts of population, was stressed. Immediate immunization was recommended of all children over 9 months of age against diphtheria and smallpox. It was suggested that the use of unexpended balances in maternal and child health funds be used for this purpose. It was urged that this nation-wide immunization be completed by May 1, 1942.

The following letter in regard to the position of pediatricians in the present war and defense organization will be of interest to all.

OFFICE FOR EMERGENCY MANAGEMENT

Office of Defense Health and Welfare Services

WASHINGTON, D. C.

January 30, 1942

Dr. Joseph Stokes, Jr.
1740 Bainbridge Street
Philadelphia, Pennsylvania

Dear Doctor Stokes:

Your letter to Colonel Lull, Office of the Surgeon General, has been referred to this office.

I realize that the pediatrist will, in a large measure, be dislocated to military and government agencies where their services will not be strictly along pediatric lines. We are, however, setting aside pediatrists for service in the Children's Bureau and the Office of Civilian Defense with relation to practice incident to encampments of women and children taken from congested sections. We trust that those who will be in military service will be assigned where their experience in infectious diseases may be used to the greatest advantage. Under the order setting up this office, the President has charged us with the equitable distribution not only in the military and governmental services, but also in the industrial and civil agencies requiring medical assistance. For this reason, we recommend that pediatrists associate with such agencies in order that they may be certified by our State chairmen as being engaged in essential capacities. These men will under these circumstances be deferred. I would emphasize, however, that the majority of those in essential capacities should be over 45, or if under 45, those physically disqualified for military service. We shall attempt to keep you informed through all State and National journals in the form of publicity releases from the Procurement and Assignment Service.

Thanking you for your interest in this matter, I remain

Sincerely yours,

(Signed) Sam F. Seeley
Sam F. Seeley
Executive Officer,
Procurement and Assignment Service

Dr. Frank Leech, of Washington, D. C., Emeritus Fellow of the Academy, died Feb. 7, 1942.

Erratum

In the Panel Discussion on Clinical Aspects of Growth and Development, February issue of the Journal, page 261, seventh line from the bottom, "tryptophane and arginine deficiency" should read "tryptophane and *lysine* deficiency."